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(71) Applicant *(for all designated States except US)*: DEXXON LTD. [IL/IL]; P.O. Box 50, 38100 Hadera (IL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LERNER, Itzhak, E. [IL/IL]; 32 Wolfson St., 49541 Petach Tikva (IL). FLASHNER, Moshe [IL/IL]; Hafetz Mordechai St. 15, 49313 Petach Tikva (IL). PENHASI, Adel [IL/IL]; Haneviim St. 45/14, 59674 Bat Yam (IL).

(74) Agent: FRIEDMAN, Mark, M.; Beit Samueloff, Haomanim St. 7, 67897 Tel Aviv (IL).

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(54) Title: LOCAL DELIVERY OF DRUGS TO THE COLON FOR LOCAL TREATMENT OF COLONIC DISEASES

(57) Abstract

A composition and method for the treatment of polyp and colon cancer is described, such composition and method providing for the colonic delivery and/or preferential metabolism of a drug or desired agent, especially an NSAID, in the colon of the patient in need of such treatment.

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Local Delivery of Drugs to the Colon for Local Treatment of Colonic Diseases

Field of the Invention

The invention is in the field of polyp and colon cancer chemoprevention and chemotherapy.

Background of the Invention

Local Treatment of Colonic Diseases such as Colorectal Polyps

The colon is part of the alimentary tract and may be affected by specific diseases which require specific treatments. Treatment of such colonic diseases preferably involves the local administration of drugs to the colon. The effect of the drug is preferably restricted as much as possible to the colon for certain drugs, in which the systemic effects of the drug would be disadvantageous. However, for other such colonic diseases and corresponding drug treatments, the systemic effect is an important component of the treatment of the disease, and is therefore both desirable and necessary. Thus, the type of delivery system for the administration of drugs to the colon is clearly important for the treatment of colonic disease, whether for local treatment alone, or for a combination of local and systemic treatment.

As an illustrative example of diseases of the colon, colorectal polyps are a significant, and even fatal, colonic disease for which more effective treatments are clearly necessary. A colorectal polyp is a circumscribed mass of tissue that projects above the surface of the bowel mucosa. It is classified as pedunculated or sessile, depending on whether it contains a discrete stalk. While most small polyps are asymptomatic lesions detected only by screening or diagnostic studies, larger polyps, greater than 10 mm, may ulcerate and cause intestinal bleeding, as well as have malignant potential.

Colorectal polyps are extremely common in adults in Western countries; they are found in more than 30% of autopsies conducted on people greater than 60 years of age (Correa P., *Gastroenterology* 77:1245-1251 (1979)). The colonic polyp has been implicated as a precursor in the development of colorectal cancer (Morson B.C., *Cancer 34*:845-850 (1974)). Current data suggest a polyp to cancer sequence, with colorectal neoplasmic changes as a continuous process

from normal mucosa, to adenoma, and then to carcinoma (Schottenfeld, D. & Winawer, S.J., *Cancer: Epidemiology and Prevention*, Philadelphia, W.B. Saunders, 703-727 (1982)).

Histologically, polyps are classified as neoplastic, i.e., adenomas, with malignant potential or as non-neoplastic, known as benign adenomas (Fenoglio, C.M. & Pascal, R.R., *Cancer 50*:2601-2608 (1982)). Approximately 70% of polyps removed at colonoscopy are adenomas, (Konishi, F. & Morson, B.C., *J. Clin. Pathol. 35*:830-841 (1982)) with the potential to become larger than 10 mm, and therefore, having the probability of becoming tumorigenic. It is, therefore, of great importance to identify colonic polyps and to treat them before they can become malignant.

Most commonly, polyps are described as sporadic, arising spontaneously in about a quarter of the population by age 50, with the prevalence increasing with age, and which may or may not result in colorectal cancer (Winawer, S.J., *et al., Gastroenterology 112*:594-642 (1997)). Familial adenomatous polyposis (FAP), on the other hand, is an autosomal dominant, inherited disorder, characterized by the presence of hundreds of adenomatous polyps in young adults and in the eventual development of colorectal cancer (Schussheim, A., *et al., Gastroenterol. Nutr. 17*:445-448 (1993)).

Colonoscopy is considered the best method for detecting polyps accurately, especially those measuring less than 10 mm in diameter (Rex, D.K., *et al., Gastroenterology 112*:17-23 (1997)). Most polyps found during colonoscopy can be completely and safely removed by electrocautery (fulguration) (Knutson, C.D. & Max, M.H., *Arch Surg 114*:30-435 (1979)). Some complications, however, may develop during colonoscopy, most commonly perforation and bleeding, occurring in 0.1 to 0.2% of patients (Rankin, G.B., *Gastrointestinal Endoscopy*, Philadelphia, W.B. Saunders, 875-878 (1987)). In addition, it is not always possible to detect all polyps using colonoscopy because of the anatomy of the colon. In fact, in a recent study, it was shown that a carefully performed complete colonoscopy by an experienced examiner will miss an average of about 24% of polyps that are less than 10 mm in diameter (Rex, D.K., *et al., Gastroenterology 112*:24-28 (1997)).

Non-Steroidal Anti-Inflammatory Drugs and Colorectal Polyps

To overcome the current technical limitations of colonoscopy, and to avoid the need for surgical procedures, extensive research has been focused during the past decade on finding pharmacologic agents that might be used to treat or prevent colorectal polyps. Especially, the effect of non-steroidal inflammatory drugs (NSAIDs) on colorectal polyps has become of

interest.

Epidemiological studies have shown that chronic aspirin use is associated with a 50-70 percent reduction in the incidence of colorectal cancer (Logan, R.F.A., *et al., Br. Med. J. 307*:285-289 (1993); Rosenberg, L., *et al., J. Natl. Cancer Inst. 83*:355-358 (1991); Thun, M.J., *et al., New Engl. J. Med. 325*:1593-1596 (1991); Suh, O., *et al., Cancer 72*:11171-1177 (1993); Peleg II *et al., Arch. Intern. Med. 154*:394-399 (1994)). In addition, multiple animal studies have documented a chemoprotective effect of selected NSAIDs as judged by a reduction in the frequency and number of premalignant and malignant lesions (Reddy, B.S., *et al., Cancer Res. 50*:2562-2568 (1990); Reddy, B.S., *et al., Carcinogenensis 14*:1493-1497 (1993); Rao, C.V., *et al., Cancer Res. 51*:4528-4534 (1991); Craven, P.A., & DeRuberis, F.R., *Carcinogenesis 14*:541-546 (1992); Northway, M.G., *et al., Cancer 66*:2300-2305 (1990); Moorghen, M., *et al., J. Pathol 156*:341-347 (1988); Reddy, B.S., *et al., Cancer Res. 47*:5340-5346 (1987); Reddy, B.S., *et al., Carcinogenesis 13*:1019-1023 (1992); Skinner, S.A., *et al., Arch. Surg. 126*:1094-1096 (1991)). In a recent case study of a patient with villous adenomas of the cecum, who refused surgical resection, a course of NSAID therapy, using piroxicam, 30 mg weekly, showed dramatic and sustained regression of the premalignant adenomas for up to 20 months (Gowen, G.F., *Dis. Colon Rectum 39*:101-102 (1996)). In clinical studies of familial adenomatous polyposis, using the NSAID, sulindac, at a daily dose of 300 mg, taken systemically, it was shown that the number and size of colonic polyps was significantly decreased (Giardelio, F.M., *et al., New Engl. J. Med. 328*:1313-1316 (1993); Labaylle, D., *et al., Gastroenterology 101*:635-639 (1991); Waddell, W.R., *et al., Am. J. Surg. 157*:175-179 (1989)). In a small pilot study, in which sulindac or piroxicam was used against sporadic colonic polyps, however, there was no similar regression of adenomatous polyps (Ladenheim, J., *et al., Gastroenterology 108*:1083-1087 (1995); Hixson, L.J., *et al., Am. J. Gastroenterol 88*:1652-1656 (1993)). These results, however, were disputed in a more recent multicenter study of nearly 100 patients, with sporadic polyps of 4-12 mm. When sulindac, 300 mg daily, or sulindac, 150 mg daily, or placebo, were given for one year, it was demonstrated that sulindac, regardless of dose, induced regressions and prevented the progression of sporadic colorectal adenomas (DiSario, J.A., *et al., Gastroenterology 112* (Suppl):555A (1997)).

NSAIDs and Apoptosis

The precise mechanism responsible for the anti-neoplastic effect of NSAIDs is unknown. A number of recent publications have suggested that NSAIDs may be accomplishing these chemoprotective effects by induction of apoptosis, the "programmed cell death" phenomenon (Savill, J., *Eur. J. Clin. Invest. 24*:715-723 (1994); Thompson, C. B., *Science 267*:1456-1462 (1995); Bright, J. and Khar, A., *Biosci Rep. 14*:67-81 (1994)). In 1965, Lockshin and colleagues introduced the concept of "programmed cell death" to describe the phenomenon that had long been observed in embryogenesis where certain predetermined cells in the embryo would die at a particular stage during development (Lockshin, R. A. and Williams, C. M. *J. Insect Physiol. 11*:123-133 (1965)). In 1972, Kerr *et al.*, linked this concept with a mode of cell death, defined on strict morphological criteria such as the detachment of a cell from its substratum, coupled by the fragmentation of the nucleus and cytoplasm, in a process which, they termed "apoptosis." (Kerr, J. F. R., *et al., Br. J Cancer 26*:239-257 (1972)). This active cell death, under tight genetic control, is found in all tissues, and is responsible both for regulating cell number and type, as well as for disposing cells with damaged or mutant DNA. Defects in apoptosis, however, can lead to cancer, autoimmune disease and neurodegeneration (Pritchard, D. and Watson, A. J. M., *Pharmacol Ther. 72*:149-169 (1996)).

Defective apoptosis has been implicated in the pathogenesis of colorectal cancer. In 1995, Bedi *et al.* quantified the amount of apoptosis in frozen sections of biopsies of colorectal epithelium from normal mucosa, adenomas from patients with familial adenomatous polyposis, sporadic adenomas, and carcinomas by *in situ* nick end labeling of histopathological specimens cultured for up to 24 hours on plastic. There was progressive inhibition of apoptosis during the transformation of normal epithelium into carcinomas (Bedi, A., *et al., Cancer Res. 55*:1811-1816 (1995)).

Additionally, other studies support the contention that NSAIDs may exert their effect on colorectal polyps and carcinoma by inducing apoptosis. Pasricha *et al.* investigated the rate of proliferation and apoptosis in the flat colorectal mucosa of patients with familial adenomatous polyposis after treatment with sulindac. No effects on proliferation were found, but the sulindac-treated group showed increased levels of colonic mucosal apoptosis (Pasricha, P. J., *et al., Gastroenterology. 109*:994-999 (1995)). Piazza *et al.* similarly demonstrated the induction of apoptosis in an HT-29 colon adenocarcinoma cell line following sulindac administration, but found no evidence of cell proliferation or differentiation (Piazza, R., *et al., Cancer Res. 55*:3110-3116 (1995)). In a clinical study, Lee found that there were increased levels of apoptotic bodies

in colonic biopsies from patients with diclofenac-induced colitis (Lee. F. D.. *J Clin Pathol 46*:18-122 (1993)).

Induction of Apoptosis via COX-2

The mechanism whereby an NSAID induces apoptosis may be attributed to its known inhibition of cyclooxygenase-2 (COX-2), an enzyme associated with the inflammatory process (Vane, J. R. and Botting, F. M., *Inflamm. Res. 44*:1-10 (1995)). Prostaglandins are synthesized by the cyclooxygenase enzyme, of which there are two known isoforms, COX-1 (Miyamoto, T., *et al., J. Biol. Chem. 251*:2629-2636 (1976)) and COX-2 (Simmons, D. I., *et al., Proc. Natl. Acad. Sci. USA 86*:1178-1182 (1989)). COX-1 is a constitutive enzyme expressed in many tissues including the gastric mucosa, whereas COX-2 is an inducible enzyme expressed in fibroblasts, macrophages and other cell types in inflammation (Masferrer, J. L., *et al., Proc. Natl. Acad. Sci. USA 89*:3917-3921 (1992); Lee, S. K., *et al., J. Biol. Chem. 267*:25934-25938 (1992)). Although NSAIDs can inhibit both COX isoforms, they are selective in their inhibition rates of these enzymes. Diclofenac sodium and piroxicam, for example, exert a strong inhibitory effect on COX-2, (Meade, E. A., *et al., J. Biol. Chem. 268*:6610-6614 (1993)) while sulindac mainly exerts an inhibitory effect on COX-1. It has been suggested that the GI side effects associated with NSAIDs relate to COX-1 inhibition, while the anti-inflammatory effects of NSAIDs, relate to COX-2 inhibition (Mitchell, J. A., *et al., Proc. Natl. Acad. Sci. USA 90*:11693-11697 (1994)).

The induction of apoptosis as a result of COX-2 inhibition by NSAIDs has been implicated in the observed effects of NSAIDs on colonic polyp regression. This possible relationship between COX-2 inhibition by NSAIDs and apoptosis was demonstrated in a study by Tsujii and DuBois (Tsujii, M. and DuBois, R. N., *Cell 83*:493-501 (1995)). They transfected a rat intestinal epithelial cell line with mRNA for COX-2, thereby inducing COX-2 over-expression, and showed that these cells showed increased adhesion to the extracellular matrix and became resistant to butyrate-induced apoptosis. The authors proposed that COX-2 over-expression enhances the induction of tumors by changes in cellular adhesion and apoptosis inhibition.

There is considerable evidence for the association of an inhibition of COX-2 activity or expression with polyp and/or tumor regression. It has been observed that the disruption of the COX-2 gene reduces the number of tumors in mice by more than six-fold. Additional treatment of these mice with drugs that selectively inhibit the COX-2 enzyme results in a marked reduction of tumor multiplicity (Oshirna, K., *et al., Cell 87*:803-809 (1996)). COX-2 expression is

elevated in intestinal tumors which develop in carcinogen-treated rats. Treatment of these animals with many different NSAIDs results in a marked decrease in tumor multiplicity (DuBois, R. N., *et al., Gastroenterology Clinics of North America 25*:773-391 (1996)). Taking all these results together, it appears likely that COX-2 may be involved in the adenoma to carcinoma sequence, and that both highly potent and selective COX-2 inhibitors (such as diclofenac sodium), and weak inhibitors of COX-2 (such as sulindac) may be effective in polyp regression in both FAP and in sporadic polyps.

Although sulindac is only a weak inhibitor of COX-2, sulindac itself may not be the active agent in these studies. Sulindac has two metabolites that are formed following extensive first pass metabolism. One metabolite, sulindac sulfone, is formed via an irreversible oxidation. The second metabolite, sulindac sulfide, is formed via a reversible reduction. These two metabolites are considered to be more active than the sulindac itself (Brogden, R.N. *et al., Drugs 16*:97-114 (1978)).

For example, the anti-inflammatory activity that is associated with sulindac is primarily attributed to the more active metabolite, sulindac sulfide (Kwan, K.C. *et al., Acta Rheumatol. Belg. 1*:168-178 (1977)). Sulindac sulfide is a potent inhibitor of COX-2 (Riendeau E. *et al., Can. J. Physiol. Pharmacol. 75*:1088-1095 (1997)). Sulindac sulfide has also been found to be effective against several biochemical markers for colon cancer. It has been demonstrated that sulindac sulfide is six times more potent than sulindac in reducing proliferation and inhibiting the cell cycle in HT-29 colon adenocarcinoma cells (Schiff, S.J. *et al. , Exp. Cell Res. 222:*179-188 (1996)) and that sulindac sulfide induced cell cycle inhibition in SW480 colon carcinoma cells (Lemoine, M. *et al., Gastroenterology 112 (suppl.)*: A673 (1997)). The other metabolite, sulindac sulfone, is relatively inactive and does not show any anti-inflammatory activity (Kelloff *et al., J. Cell Biochem. 20 (suppl.)*: 240-251 (1994)) but has shown some anti-neoplastic activity (Piazza, G.A. *et al., Gastroenterology 112 (suppl)*: A638 (1977)).

The association of NSAIDs with polyp and/or tumor regression is clear. The evidence for COX-2 involvement is very strong; however, in addition, other mechanisms may also play a role.

Local Delivery of NSAIDs to the Colon

A disadvantage of most NSAID therapy for colorectal polyps is that the NSAID is given systemically, and for long periods. Prolonged high systemic concentrations of many NSAIDs can result in other complications unrelated to the polyp treatment. For example, such NSAID users have a three-fold greater risk of developing serious GI complications over non-NSAID users. It

has been estimated that 20% to 40% of patients on systemic NSAID therapy develop peptic ulcers (Taha, A., *et al., N. Engl. J. Med. 334*:1435-1439 (1996)). It has also been estimated that 10,000 - 20,000 fatalities a year occur in the United States from NSAID-induced gastrointestinal disorders. Other adverse effects of NSAIDs include renal failure, hepatic dysfunction, bleeding and gastric ulceration. The side effects of NSAIDs are especially of concern in the elderly, the very population most at risk for the development of colonic polyps. Therefore, a need exists for an alternative method to target therapeutic concentrations of NSAIDs to the site of colonic polyps.

Sulindac, given orally as a tablet, is primarily absorbed through the gastrointestinal tract. The peak plasma concentration is reached about two hours after dosing (Swanson, B.N. *et al., Clin. Pharmacol. Ther. 32*:397-403 (1982)). As a result of sulindac's extensive first-pass metabolism to its active metabolites, the plasma concentrations of sulindac sulfide and sulindac sulfone will exceed the levels of sulindac within four hours after dosing. Thereafter, these metabolites will remain the two major components in the blood while the concentration of sulindac will rapidly taper off (Duggan, D.E. *et al., Clin. Pharmacol. Ther. 21*:326-335 (1977)).

It has been demonstrated that although sulindac that is administered orally is primarily absorbed into the blood, a certain amount reaches the colon. The sulindac that reaches the colon will be reduced by the colonic microflora exclusively to sulindac sulfide, resulting in a high lumenal concentration of sulindac sulfide in the colon (Hanif, R. *et al., Biochem. Pharmacol. 52*:237-245 (1996)). The sulindac sulfide that is formed will then be absorbed through the colon walls to the bloodstream. This premise is supported by the fact that sulindac sulfide appears in the plasma long after sulindac and sulindac sulfone have been excreted in the urine and feces and that these findings are not seen in patients who underwent a colectomy and ileostomy (Strong, H.A. *et al., Clin. Pharmacol. Ther. 38*:387-393 (1985)). It can be concluded that the intact colon plays a significant role in the sustained presence of sulindac sulfide in the blood and that delivering the entire dose of the sulindac to the colon will result in a significant enhancement of the formation of sulindac sulfide over the less active metabolite, the sulindac sulfone.

Local Delivery of Drugs to the Colon

Local delivery of drugs to the colon is both desirable and necessary to treat colonic diseases, such as colorectal polyps, as previously described. Various systems for such local drug delivery to the colon have been proposed in the background art.

U.S. 5,498,608 (Johnson, L.K.) describes the use of 2-hydroxy-5-phenylazobenzoic acid derivatives for the treatment of colon cancer. The derivatives are prodrugs that are converted into an active anti-inflammatory drug by the action of colonic bacteria. The use of these agents for the treatment or prevention of colon cancer is proposed.

U.S. 5,686,589, U.S. 5,401,774, U.S. 5,643,959, EP 485,171, EP 485,173, and EP 508,586 (Brendel, K.) describes conjugating drugs into a prodrug form with substituted fused ring phenylacetic acids as a mechanism to deliver the active agent, such as an NSAID, to a colonic polyp. Colonic bacterial enzymes then cleave the active agent from the macromolecule.

U.S. 5,686,105 and U.S. 5,686,106 (both to Kelm, G.R.) describe the use of polymers to coat an active agent for delivery to the colon. The polymers dissolve at about the time that the dosage form reaches the inlet between the small intestine and the colon, or at most, only in the proximal colon. Beyond the proximal colon, such polymers typically are completely dissolved and no longer provide a coat for the active agent. Examples of such polymers include Eudragit® L and cellulose acetate phthalate. Examples of the types of agents that can be provided to the colon in this manner include agents for the topical treatment of diseases of the colon, such as irritable bowel syndrome, Crohn's disease, ulcerative colitis and carcinomas. Examples of the specific active agents that are listed include nonsteroidal anti-inflammatory drugs, and chemotherapeutics for treatment of carcinomas.

U.S. 5,464,633 (Conte, U., *et al.*) describes a tablet that consists of a core containing the active substance, and an external layer that is able to prevent the immediate release of the active substance. The external layer can be a natural and/or synthetic polymeric substance in the class of the erodible and/or gellable and/or soluble in an aqueous medium hydrophilic polymers and adjuvant substances. Lastly, the layer is surrounded by a gastroresistant and enterosoluble coating.

However, none of these background art references teaches or suggests the local administration of the anti-colorectal polyp therapy, sulindac, specifically to the colon. Although the drug is currently administered orally, as previously noted, only a fraction of the drug actually reaches the colon. Yet it is this fraction which is metabolized to the more active metabolite, sulindac sulfide, for more effective treatment of colorectal polyps. Thus, a more effective treatment would involve the delivery of the entire dose of sulindac to the colon, although a drug delivery system for such specific local treatment is not currently available.

There is thus a need for, and it would be useful to have, a drug delivery system for specific, targeted, local treatment of colonic diseases, in which at least a significant fraction of

the drug is delivered to the colon, optionally with a second stage of systemic absorption and treatment, such that these colonic diseases are more effectively treated.

Summary of the Invention

The present invention is of a formulation for locally delivering efficacious levels of drugs to the colonic environment for local treatment of colonic disease, in which at least a significant fraction of the drug is delivered specifically to the colon. Optionally, in a second stage, at least a fraction of the drug is absorbed systemically for systemic treatment of the colonic disease state. The formulation of the present invention is considered to be particularly effective for the administration of sulindac to a subject, for example for the treatment of colorectal polyps, since the local administration of sulindac to the colon encourages the formation of the more active metabolite, sulindac sulfide.

The structure of the formulation of the present invention enables the targeted delivery of drugs to the colon, by restricting the release of the drug until the formulation enters the colon. The formulation comprises a coating over a core which contains the drug. The restricted release of the drug within the colon is provided through the structure of the coating, which features water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier. When the formulation is exposed to an aqueous environment, the particulate matter in the coat absorbs water, thus forming channels that interconnect the inner core with the outer surface of the coating. These channels allow aqueous solutions to enter the core. The advantage of such a structure is that the drug is therefore not released until the formulation is delivered locally to the colon, yet the type of release of the drug can then be determined according to the structure of the core containing the drug.

For example, if a sustained or prolonged release of the drug is desired, then preferably the core does not swell rapidly and then disintegrate, but rather releases the drug through the channels formed in the coating in a sustained manner. If the core is designed to be swellable, then preferably the degree of swelling is such that the coating does not burst.

Alternatively, if the core contains a swelling agent and a disintegrant, as the channels are formed in the coating, the core absorbs sufficient liquid so that it swells considerably, and disintegrates rapidly after the coating is breached. Therefore, the disintegration occurs essentially in a burst, the burst being sufficient to release efficacious amounts of the drug from the delivery device or system. Preferably, the swelling agent is an insoluble polymer that is capable of swelling considerably but that does not form a strong gel.

Optionally and preferably, in either case, the nature of the coating is adjusted according to the type of core and the type of release which is desired. For example, if a burst release from the core is desired, then preferably the coating contains a relatively rigid hydrophobic polymer, such that when the core swells upon entry of liquid through the channels in the coating, the internal pressure causes the coating to be destroyed in a burst effect. Alternatively, if a sustained, prolonged release from the core is desired, then preferably the coating is provided such that the drug is released through the channels formed therein. Both of these embodiments are described in greater detail below.

Examples of suitable formulations for the present invention include the colonic delivery system that is the subject of U.S. Patent 5,525,634 and U.S. Patent 5,840,332 and U.S. Appl. No. 08/969,796, each incorporated herein by reference. The colonic delivery systems described above serve as a means to target enterally administered drugs to the large intestine. When the drug-matrix composition of the invention is present in the stomach or the small intestine, its drug content is shielded by the coating and is not significantly released until arrival in the colon. Thus, one particular advantage of the formulations for the present invention is the ability to protect the active agent for release anywhere in the colon, in contrast to prior art formulations, which only reach the inlet between the small intestine and the colon, or at most, the proximal colon.

The formulation of the present invention is considered to be particularly effective for the administration of sulindac to the subject for local treatment of the colon, particularly for the treatment of colorectal polyps. Such local treatment enhances the amount of sulindac which is converted into the more active metabolite, sulindac sulfide, when compared to the amount that is converted into sulindac's less active metabolite, sulindac sulfone, by minimizing the amount of sulindac that is absorbed into the bloodstream and by maximizing the amount of sulindac that is delivered to the colon - at which location the sulindac is preferentially metabolized into sulindac sulfide by the colonic environment and absorbed therefrom. Thus, the present invention also encompasses a method for the administration of sulindac to a patient in need of the same wherein the majority, if not all, of the dose of sulindac that is administered to such a patient is delivered to the colon of the patient.

Such a method is also generally useful for the delivery of a desired agent in which the colonic contents or colonic tissue metabolize the desired agent to a more desired form, for example, a more active metabolite as in the case of sulindac. Such a more desired form is thus synthesized in a preferential manner for providing a locally higher concentration by targeted

delivery for local treatment of the colon, than when the drug is administered systemically or orally in a conventional manner. Optionally and preferably, these methods and compositions are useful for the administration of orally administered drugs or chemical agents that are processed to active metabolites in the colonic environment for a subject who suffers from impaired liver function. This impaired function impairs normal hepatic metabolism of drugs to active metabolites. Metabolism in the colon can serve an alternative for metabolism in the liver for such drugs in these subjects.

Other useful and desired agents which may be more advantageously administered to the colon through targeted delivery for local treatment include an NSAID (non-steroidal anti-inflammatory drug): a COX-2 inhibitor, whether as the desired agent itself or as the metabolite of such an agent: anti-cancer drugs: steroids: 5HT 3 antagonists: 5HT 4 antagonists: 5HT 4 agonists: and the like.

With regard to agents such as anti-cancer drugs. an optional but further preferred embodiment of a method according to the present invention is possible. in which the drug is administered locally to the colon for local treatment in a first stage. In a second stage, the drug is also absorbed systemically for systemic treatment of the colonic disease state. Such a method is particularly preferred for the treatment of cancers of the colonic tissue, since if the cancerous cells have metastasized beyond the colon, the drug must also be absorbed systemically for effective treatment of the cancer. Such metastasized cells can be described as a "colonic disease state", in that these cells are part of the colonic cancer and must therefore be treated as part of the disease of the colon. regardless of their precise location in the body of the subject. Such a two-stage method of treatment is not effectively provided by the background art. since it requires both targeted delivery to the colon and systemic absorption of sufficient amounts of the drug for effective treatment of the colonic cancer.

For example, the following method could be used for the two-stage treatment of the disease condition, in which at least a portion of the disease condition is localized at a colon of the subject and at least a portion of the disease condition is localized outside of the colon of the subject. First, a composition containing the drug of choice is orally administered to the subject. Next, a majority of the drug is released from the composition at the colon of the subject. Then, the portion of the disease condition localized at the colon with the drug is treated. Next, at least a portion of the drug is absorbed through the colon for systemic action in the subject. The portion of the disease condition which is localized outside of the colon is then treated with the systemically absorbed drug.

Colonic diseases for which the formulations of the present invention may be effectively used for the local administration of therapeutic agents to the colon include, but are not limited to, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), Crohn's disease, polyps, ulcerative colitis, precancerous and cancerous lesions, constipation, and dysfunctions of colonic motility.

Definitions

In the description that follows, a number of terms used in pharmacology are extensively utilized. In order to provide a clear and consistent understanding of the specification and claims, and the scope to be given such terms, the following definitions are provided.

By the term "colon" is meant that part of the large intestine that extends from the cecum to the rectum. The cecum is the blind pouch in which the large intestine begins and into which the ileum opens from one side.

By the term "matrix" is meant a surrounding substance within which something else is contained. In a preferred embodiment, the matrix is a material comprising a natural polymer that can be modified or unmodified, but that, in its unmodified form, is resistant to enzymatic degradation in the stomach and small intestine by pancreatic enzymes. Preferably the matrix is a natural polymer that is not enzymatically degraded in the stomach, for example, a calcium pectinate-pectin polymer which is preferentially degraded in the colon, as opposed to the stomach and small intestine.

By the term "NSAID" is meant a Non-Steroidal Anti-Inflammatory Drug; that is, any drug classified as having non-steroidal anti-inflammatory properties. An NSAID acts by impairing prostaglandin synthesis. The term "NSAID" is intended to be interpreted broadly and is not limited in terms of chemical composition.

By the term "treat", as in "treat a patient" or "treat a subject", is meant to give medical aid to such patient, especially, for the purposes of preventing the development of, or preventing the worsening of, an undesired physiological or medical condition, or for the purposes of ameliorating such condition in such patient, either human or animal. Unless otherwise stated, the term "treat" is not limited to any particular length of time or to any particular level of dose.

By the term "more active metabolite" is meant a metabolite of a drug that gives enhanced desired clinical effect in comparison to the effect that is achieved by the unmetabolized drug.

By the term "precancerous lesion" is meant a lesion that exhibits histologic changes that are associated with an increased risk of cancer development. Examples include adenomatous

polyps of the colon. Certain syndromes that commonly display precancerous lesions are also referred to by the term "precancerous" including dysplastic nevus syndrome and the colonic polyposis syndromes. The term "precancerous lesions" refers to such lesions or syndromes whether or not the lesions are clinically identifiable.

By the term "sensitive to treatment" is meant that a target that it is desired to treat (for example, the cells of a precancerous or cancerous lesion) directly or indirectly respond in a beneficial manner to the influence of an agent, especially, an agent that has an antiproliferative effect on such cells.

"High risk" polyps patients are patients who have had three or more polyps found during a colonoscopic examination.

Hereinafter, all drugs described below are assumed to also include pharmaceutically acceptable salts and derivatives, and prodrugs thereof.

Brief Description of the Drawings

Figure 1 shows the averaged data for sulindac in three different treatments: Treatment A: One tablet sulindac CDS; Treatment B:Two tablets of sulindac CDS; and Treatment C: Two tablets of commercial sulindac

Figure 2 shows the averaged data for the concentration of sulindac sulfide in the blood in the three treatments listed in the legend to Figure 1.

Figure 3 shows the averaged data for the concentration of sulindac sulfone in the blood in the three treatments listed in the legend to Figure 1.

Detailed Description of the Preferred Embodiments

The present invention is of a formulation for locally delivering efficacious levels of drugs to the colonic environment for local treatment of colonic disease, in which at least a significant fraction of the drug is delivered specifically to the colon. Optionally, in a second stage, at least a fraction of the drug is absorbed systemically for systemic treatment of the colonic disease state. The formulation of the present invention is considered to be particularly effective for the administration of sulindac to a subject, for example for the treatment of colorectal polyps, since the local administration of sulindac to the colon encourages the formation of the more active metabolite, sulindac sulfide. Other drugs which may be so administered include, but are not limited to, anti-cancer drugs, NSAID's and steroidal drugs.

The structure of the formulation of the present invention enables the targeted delivery of drugs to the colon, by restricting the release of the drug until the formulation enters the colon. The formulation comprises a coating over a core which contains the drug. The restricted release of the drug within the colon is provided through the structure of the coating, which features water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier. When the formulation is exposed to an aqueous environment, the particulate matter in the coat absorbs water, thus forming channels that interconnect the inner core with the outer surface of the coating. These channels allow aqueous solutions to enter the core. The advantage of such a structure is that the drug is therefore not released until the formulation is delivered locally to the colon, yet the type of release of the drug can then be determined according to the structure of the core containing the drug.

In particular, two preferred embodiments for the structure of the core are contemplated, which preferably include adjustments to the coating itself in order to promote the desired action of the core. However, it should be noted that optionally, any suitable conventional core could be used with the coating according to the present invention.

In a first embodiment, for sustained or prolonged release of the drug, preferably the core does not swell rapidly and then disintegrate, but rather releases the drug through the channels formed in the coating in a sustained manner. If the core is designed to be swellable, then preferably the degree of swelling is such that the coating does not burst. The coating is then preferably adjusted to permit the drug to be released through the channels formed therein.

The core material includes, but is not limited to combinations of pectin, calcium pectinate, hydroxypropylmethylcellulose, lactose, starch, polyvinylpyrrolidone, microcrystalline cellulose, calcium phosphate, guar gum, and normal pharmaceutical additives and excipients (see Handbook of pharmaceutical Excipients, 2nd ed., Wade, A. and Weller, P. J., eds., American Pharmaceutical Association (1994)).

In preferred embodiments, the core material comprises calcium pectinate, hydroxypropylmethylcellulose, microcrystalline cellulose, starch, or any combination thereof. Alternate core materials include, but are not limited to, carboxymethylcellulose, lactose, polyvinylpyrrolidone, guar gum, alginic acid, sodium alginate, carrageenan, or any standard tablet excipient known to those in the art (see Handbook of Pharmaceutical Excipients, 2nd ed., Wade, A. and Weller, P. J., eds., American Pharmaceutical Association (1994)).

The particulate matter includes, but is not limited to, polysaccharides. Such polysaccharides include, but are not limited to calcium pectinate, calcium alginate, calcium

xanthate, any metal salt of a polysaccharide containing an acid group where the salt renders the polysaccharide insoluble in water, any water insoluble polysaccharide (e.g. cellulose or microcrystalline cellulose), any polysaccharide rendered insoluble by interacting with a poly-cation or poly-anion, and any covalently crosslinked polysaccharide where said crosslinking renders the polysaccharide insoluble in water. Such crosslinking agents include, but are not limited to, glutaraldehyde, formaldehyde, epichlorohydrin, diacid chlorides, diisocyananates, diacid anhydrides, and diamines.

The coating material may optionally contain a plasticizer to improve its properties as is known in the art. The coating may be optionally coated with an outer coating of a normal enteric coating, as known in the art, if the coating material or the particulate is affected by the acid conditions of the stomach. Further outer coatings include, but are not limited to, coatings to ease swallowing or mask taste.

In preferred embodiments, the coating material comprises calcium pectinate and Eudragit E™, Crospovidone and Eudragit E™, or calcium pectinate and ethylcellulose. In this embodiment the particulate matter comprises calcium pectinate or Crospovidone while the Eudragit E™ or ethylcellulose comprises the water insoluble carrier.

The water insoluble carrier may or may not include a plasticizer according to the normal properties of a film as known to those skilled in the art. In alternate embodiments, the coating includes, but is not limited to, any combination of a water-insoluble polysaccharide, water-insoluble crosslinked polysaccharide, a water-insoluble polysaccharide metal salt, a water-insoluble crosslinked protein or peptide, a water- insoluble crosslinked hydrophilic polymer in a dried powder form as the particulate and any hydrophobic polymer coating known in the art as the water-insoluble carrier.

Specific examples of the particulate material include, but are not limited to, microcrystalline cellulose, chitosan, calcium or zinc alginate, calcium xanthate, guar gum borax complex, glutaraldehyde- or formaldehyde-crosslinked guar gum, glutaraldehyde- or formaldehyde- crosslinked dextran, epichlorohydrin-crosslinked dextran, glutaraldehyde- or formaldehyde-crosslinked soluble starch, glutaraldehyde-or formaldehyde-crosslinked hydrolyzed gelatin, glutaraldehyde- or formaldehyde-crosslinked gelatin, glutaraldehyde- or formaldehyde- crosslinked collagen, any insoluble complex of a polysaccharide and a protein or peptide, glutaraldehyde- or formaldehyde-crosslinked hydroxypropylcellulose, glutaraldehyde- or formaldehyde-crosslinked hydroxyethylcellulose, glutaraldehyde- or formaldehyde-crosslinked

hydroxypropylmethylcellulose, or any of the carbomers (crosslinked acrylic acid polymers).

Specific examples of the water-insoluble carrier include, but are not limited to, Eudragit E™, Eudragit NE™, Eudragit RL™, Eudragit RS™, ethylcellulose, zein, and waxes.

In a preferred embodiment a modified pectin is used for the matrix. The pectin is modified to reduce its solubility (hydrophilicity), at acidic gastric pH values and at neutral intestinal pH values. A pectin of low methoxy content (i.e. degree of esterification <40%) is reacted with a divalent metal salt, preferable calcium chloride, in an alcohol:water mixture. The alcohol is most preferably either ethanol or isopropyl alcohol. Other cations, such as magnesium, strontium, aluminum, and iron salts can replace the calcium in modifying the pectin for use in the matrix formulation of the drug.

In a highly preferred embodiment, the drug is formulated with calcium pectinate, low methoxy pectin and hydroxypropylmethylcellulose in suitable amounts. The calcium pectinate can range from 20% to 40%, the pectin from 10% to 30%, the hydroxypropylmethylcellulose from 10% to 35% and the drug from 0.5% to 50%. In a most highly preferred example of this embodiment, the percentages are calcium pectinate 22%, low methoxy pectin 22%, hydroxypropylmethylcellulose 13% and sulindac 43%. The tablets further contain magnesium stearate and may be coated with a standard enteric coating based on Eudragit L.

After preparing the pectin matrix, the matrix is combined with a drug. Methods are known for formulating a composition to allow controlled release of the chosen pharmaceutical compound. Using these and other known methods, compositions of the desired pharmaceutical compound may be formulated with the polymers of the present invention. Examples of such methods are disclosed in Saffran *et al.*, *Science 233*:1081-1084 (1986) and Levine *et al.*, *Gastroenterology 92*:1037-1044 (1987).

Specific embodiments of prepared formulations of the compositions of the invention, include, for example, matrix-drug tablets, especially tablets prepared by compression (compressed tablets); matrix-drug pellets, either free or packed in gelatin capsules, or any other means allowing oral administration; matrix-drug nanoparticles, either free or packed in gelatin capsules or any other means allowing oral administration; and multi-layered tablets which comprise cored drug, coated with biodegradable polymers, the polymeric layer being prepared, for example, by spray-coating, molding or double-press procedure. All of these techniques for preparation of such formulations are well known in the art.

In a further embodiment of this invention, the drug is incorporated in a core which can be

a colonic delivery core as above or a conventional tablet core. The drug can be present in this core at a level of 0.1 to 99%. The core is further coated with a coating suitable for controlled delivery in the gastrointestinal tract as is described in U.S. Patent 5,840,332, incorporated herein by reference. The concentration of particles, the size of the particles and the coating thickness is controlled to effect colonic delivery. In a preferred embodiment, the water-insoluble coating is Eudragit E, the water-insoluble hydrophilic particulate matter is calcium pectinate, the particle size is <150 microns. Eudragit E is a dimethylaminoethylmethacrylate/methylmethacrylate and butylmethacrylate copolymer - a copolymer that is based on neutral methacrylic acid esters and diethylaminoethyl methacrylate esters in which the polymer is cationic in the presence of acids. The particulate matter is preferably present in 50-90% by weight and the coating thickness is preferably between 5 and 150 microns. In a most preferred embodiment, the calcium pectinate is present at 70% by weight and the coating thickness is about 40 microns and the core contains 100 mg sodium diclofenac.

In a most highly preferred embodiment, the drug is preferentially metabolized in the colon to a more active or more selective metabolite. In an example of such a most highly preferred embodiment, 150 mg sulindac is incorporated in a colonic delivery matrix core of 9 mm diameter containing 77.5 mg calcium pectinate, 77.5 mg low methoxy pectin, 45 mg hydropropylmethylcellulose and 1.8 mg magnesium stearate. This core was further coated with 3:7 wgt:wgt Eudragit E:calcium pectinate of particle size <150 microns at a coating thickness of about 35 microns. This system was further coated with a standard enteric coating of Eudragit L. The oral administration of such compositions results in the sulindac being delivered to the colon where it is preferentially metabolized to sulindac sulfide, a more active metabolite with considerable COX-2 activity.

Another embodiment of this invention also includes a multi-layer slow release composite. More particularly, in this embodiment, this invention relates to a multi-layered slow release composite wherein layers having a physiologically active substance encapsulated therein alternate with layers having no physiologically active substance encapsulated therein.

In the second and alternative embodiment, disintegration occurs essentially in a burst, the burst being sufficient to release efficacious amounts of the drug from the delivery device or system. For this embodiment, the core contains a swelling agent and a disintegrant. Preferably, the swelling agent is an insoluble polymer that is capable of swelling considerably but that does not form a strong gel. More preferably, the coating is adjusted to promote the burst effect by containing a relatively rigid hydrophobic polymer, such that when the core swells upon entry of

liquid through the channels in the coating, the internal pressure causes the coating to be destroyed in a burst effect. In a particularly preferred implementation of this embodiment, the essential components of the core are (1) an insoluble polymer that is capable of swelling considerably but that does not form a strong gel (*i.e.*, hydrogel), (2) a disintegrant, and (3) a hardness enhancer.

Useful water insoluble polymers include, but are not limited to, an insoluble metal salt of a polysaccharide such as calcium pectinate or calcium alginate, or a heavily cross-linked polysaccharide such as glutaraldehyde-cross-linked guar gum, pectin, alginic acid, or other vegetable gum. In a preferred embodiment, the polymer is calcium pectinate or calcium alginate. In a highly preferred embodiment, calcium pectinate is most preferred. When calcium pectinate is used, it is preferably present in the core at a range of around of 20-70% (weight/weight); more preferably, 30-60%.

Another example of a useful water insoluble polymer is a heavily cross-linked polysaccharide. Preferred embodiments of such polysaccharides include glutaraldehyde cross-linked guar gum, pectin, and alginic acid. Other useful polymers include other cross-linked vegetable gums.

If a polymer is cross-linked, the cross-linking should be such that the polymer swells considerably but does not form a coherent gel. The proper degree of cross-linking (*i.e.*, "heavy" within the context of the invention) means that a large percent of the monomer units are cross-linked, or alternatively, that there are many cross-links per polymer chain. The absolute degree of cross-linking is flexible, and is based on the desired result as explained above. Thus, cross-linking can be correlated with hydrogel formation by assays known in the art.

Useful disintegrants include, but are not limited to, Crospovidone. Other disintegrants are known in the art and would be known to the ordinary skilled artisan. A reference listing disintegrants and other types of dosage components can be found, for example, in *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, Herbert A. Lieberman, *et al.*, eds., Second Edition, Marcell Dekker Inc., New York, NY (1984). In a highly-preferred embodiment, Crospovidone is the preferred agent. The Crospovidone is preferably present in the core at a range of about 5-12% (weight/weight) and most preferably around 10%.

Useful hardness enhancers include, but are not limited to, microcrystalline cellulose (Emcocel™), starch, polyvinylpyrrolidone, low molecular weight hydroxypropylcellulose, and low molecular weight hydroxypropylmethylcellulose. In a preferred embodiment,

microcrystalline cellulose (MCC) is the hardness enhancer. MCC is preferably present in the core at a range of about 20-50% (weight/weight), and most preferably 30-40%.

In a preferred embodiment, the form of the core includes tablets and pellets, especially compressed tablets and matrix tablets. The core optionally contains lubricants, such as magnesium stearate or talc, glidants, such as fumed silica, binders for granulates, such as ethylcellulose, polyvinylpyrrolidone, and pectin, with ethylcellulose (NF-7) as the binder. However, other binders are known in the art (*Pharmaceutical Dosage Forms: Tablets*, Vol. 1, Herbert A. Lieberman, *et al.*, eds., Second Edition, Marcell Dekker Inc., New York, NY (1984)). Thus, the core material can include normal pharmaceutical additives and excipients. (See *Handbook of Pharmaceutical Excipients*, 2nd ed., Wade, A. and Weller, P.J., eds., American Pharmaceutical Association (1994)).

Combinations of materials are also useful for the core. For example, additional useful core materials include, but are not limited to, combinations of calcium pectinate, starch, polyvinylpyrrolidone, microcrystalline cellulose, calcium phosphate, and cross-linked guar gum. In preferred embodiments, the core material includes a combination of calcium pectinate, starch, microcrystalline cellulose, and calcium phosphate.

In a preferred embodiment, the core material includes calcium pectinate, Crosprovidone, microcrystalline cellulose, starch, or any combination thereof. Alternate core materials include, but are not limited to, carboxymethylcellulose, calcium alginate, cross-linked guar gum, cross-linked polysaccharide, cross-linked vegetable gum, cross-linked hydrophilic polymer, alginic acid, sodium alginate, carrageenan, or any other standard tablet excipient known to those in the art. (See *Handbook of Pharmaceutical Excipients*, 2nd ed., Wade, A. and Weller, P.J., eds., American Pharmaceutical Association (1994)).

The coating comprises a material that is not soluble, or minimally soluble, in aqueous solution, within which material a hydrophilic, non-water-soluble, particulate is embedded. The essential features of the coating are a relatively rigid hydrophobic polymer, embedded with particles of an insoluble hydrophilic polymer that allow entry of water in a controlled fashion. The particles preferably have the ability to swell. The coating serves to control the rate of liquid entry into the tablet. Factors that influence the rate of liquid intake are the weight percent of hydrophilic particles, the size of the particles, the swelling characteristics of the particles, and the degree of hydrophilicity. The core can also influence the rate of water intake for a given coating thickness. A relatively high concentration of water soluble salts in the core (relative to the outside of the tablet) causes a high osmotic gradient across the coating membrane, enhancing

uptake of liquid.

The essential features of the preferred embodiment of a coating for the burst formulation of the present invention are that it contain (1) a relatively rigid hydrophobic polymer, and (2) insoluble hydrophilic polymer particles, that preferably swell in liquid, and that allow the entry of liquid into the core in a controlled fashion by means of channels formed thereby. The polymer should be rigid enough so that when it is cast as a film, including the non-soluble hydrophilic particle, the "toughness" parameter -- which is the area under the stress-strain curve in which the polymer does not tear (units are energy/area) -- will give values of 0.009-0.21 MPa.

Useful relatively rigid hydrophobic polymer includes, but are not limited to, ethylcellulose, Eudragit RL™, Eudragit RS™, and zein. Ethylcellulose is the preferred polymer. Eudragit RL™ is a dimethylaminoethylacrylate/ ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20. This polymer corresponds to USP/NF "Ammonio Methacrylate Copolymer Type A."

Eudragit RS™ is an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40. This polymer corresponds to USP/NF "Ammonio Methacrylate Copolymer Type B."

Eudragit L™ is a methacrylic acid/methylmethacrylate or ethylacrylate copolymer, an anionic copolymer based on methacrylic acid and methylmethacrylate or on methacrylic acid and ethylacrylate. The ratio of free carboxyl groups to the ester groups is approximately 1:1. This polymer corresponds to USP/NF "Methacrylic Acid Copolymer Type A and Type C."

The insoluble hydrophilic particles in the coating are preferably particles that will swell. Examples of useful substances for such particles includes, but is not limited to, polysaccharides. Such polysaccharides include, but are not limited to particles of calcium pectinate, calcium alginate, calcium xanthate, any metal salt of a polysaccharide containing an acid group where the salt renders the polysaccharide insoluble in water, any water insoluble polysaccharide (*e.g.*, cellulose or microcrystalline cellulose), any polysaccharide rendered insoluble by interacting with a poly-cation or poly-anion, and any covalently crosslinked polysaccharide where said crosslinking renders the polysaccharide insoluble in water. Such crosslinking agents include, but are not limited to, glutaraldehyde, formaldehyde, epichlorohydrin, diacid chlorides,

diisocyananates, diacid anhydrides, and diamines. In a highly-preferred embodiment, the particulate matter is, or contains, calcium pectinate.

The coating material may optionally contain a plasticizer to improve its properties as is known in the art.

The coating that is next to the core and surrounds the core may be optionally coated with its own, outer coating, especially an enteric coating, as known in the art. This is especially useful if the core's coating material or the particulate embedded therein is adversely affected by the acid conditions of the stomach. Additional outer coatings include, but are not limited to, coatings to ease swallowing or mask taste.

In preferred embodiments, the coating material that is next to the core and into which the particles are embedded contains calcium pectinate (as the hydrophilic non-soluble particles) and Eudragit RL™ or Eudragit RS™ (as the hydrophobic film), Crospovidone and Eudragit RL™ or Eudragit RS™, or calcium pectinate and ethylcellulose. In the most preferred embodiment, the coating material comprises calcium pectinate and ethylcellulose.

The water insoluble carrier may or may not include a plasticizer according to the normal properties of a film as known to those skilled in the art.

In alternate embodiments, the coating includes, but is not limited to, any combination of a water-insoluble polysaccharide, water-insoluble crosslinked polysaccharide, a water-insoluble polysaccharide metal salt, a water-insoluble crosslinked protein or peptide, a water-insoluble crosslinked hydrophilic polymer in a dried powder form as the particulate and any hydrophobic polymer coating known in the art as the water-insoluble carrier. Specific examples of useful particulate material include, but are not limited to, microcrystalline cellulose, chitosan, calcium or zinc alginate, calcium xanthate, guar gum borax complex, glutaraldehyde- or formaldehyde-crosslinked guar gum, glutaraldehyde- or formaldehyde-crosslinked dextran, epichlorohydrin-crosslinked dextran, glutaraldehyde- or formaldehyde-crosslinked soluble starch, glutaraldehyde- or formaldehyde-crosslinked hydrolyzed gelatin, glutaraldehyde- or formaldehyde-crosslinked gelatin, glutaraldehyde- or formaldehyde-crosslinked collagen, any insoluble complex of a polysaccharide and a protein or peptide, glutaraldehyde- or formaldehyde-crosslinked hydroxypropylcellulose, glutaraldehyde- or formaldehyde-crosslinked hydroxyethylcellulose, glutaraldehyde- or formaldehyde-crosslinked hydroxypropylmethylcellulose, or any of the carbomers (crosslinked acrylic acid polymers).

The core may be designed with varying rates of swellability, *e.g.*, rapid swelling,

moderately rapid, slow, etc.

Accordingly, the location of drug release is controlled by varying specific parameters such as the thickness of the outer coating, the amount of particulate embedded in the coating, the type of particulate embedded in the coating, the particle size distribution of the particulate embedded in the coating, the core carrier, the rate of core swelling, swellability of the particulate matter in the coating, hydrophilicity of the particulate matter in the coating, rate of core swelling, and salt concentration in the core.

The preferred method of preparation for this second embodiment of the formulation according to the present invention is by the preparation of a suspension of the hydrophilic, water-insoluble particulate in an alcoholic solution of a hydrophobic polymer. This suspension is spray coated onto the core tablet or capsule, for example using conventional pan coating technology.

In a preferred embodiment of the invention, the delivery system or device is a tablet that contains a core material which is a disintegrating tablet. The tablet is made with standard granulation and tableting techniques and is coated using pan coat technology. Instead of a solution, a suspension of the particulate material in a solution or fine suspension of the polymeric coating material is sprayed on the tablets. The suspension is stirred to keep it relatively homogeneous. Warm or cold air is flowed over the tablets to allow for the film to form and the tablets to dry. Suitable solvents for such polymeric solutions or suspensions are the typical solvents known to those in the art for spray coating tablets and include, but are not limited to, water, ethanol, acetone and isopropanol. Ethanol is the preferred solvent.

The core diameter can range from 1 mm to 15 mm, and is preferably 6-9 mm. The coating level can range from 2 to 50 mg/cm^2, and is preferably from 4 to 20 mg/cm^2. The percent of particulate matter in the coating can range from 1 to 95%, and is preferably 50-70%. The particle size of the particulate matter can range from 0.1 micron to 500 microns, and is preferably from 1 to 150 micions.

In particularly preferred embodiments, the delivery system or device is a 9 mm tablet of a drug (*e.g.*, sodium salicylate or sodium diclofenac), a polymer that swells (*e.g.*, calcium pectinate), an agent that causes tablet disintegration (*e.g.*, Crospovidone) and a hardness enhancer (*e.g.*, microcrystalline cellulose) coated with a suspension of one part calcium pectinate and one part ethylcellulose in 20-30 parts ethanol. The best results are obtained with calcium pectinate of particle size <149 m and a film coating of 13 mg/cm^2. This embodiment allows for delivery of a soluble drug to the colon since it affords an approximate four hour delay in drug release under *in vitro* conditions of USP Intestinal TS (*U.S. Pharmacopeia XXII National*

Formulary XVII, page 1789 (1990)) when using dissolution apparatus 2 (*U.S. Pharmacopeia XXII, National Formulary XVII*, page 1579 (1990)).

The preferred embodiment is coated with Eudragit L™ as an enteric coat to protect the calcium pectinate from the effects of the acid pH of the stomach. The enteric coat dissolves in the upper part of the small intestine. The particulate calcium pectinate starts to slowly swell as intestinal fluid enters the coating. After about four hours, channels have formed, the core has swollen and the drug is released in a burst upon tablet disintegration.

In accordance with either the sustained release embodiment or the burst release embodiment of the present invention, the water-insoluble carrier may optionally feature a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

Also in accordance with either embodiment of the formulation of the present invention, the matrix may be used in microparticles that contain the drug enclosed with them. The microparticles may have a permeable water insoluble matrix selected from proteinaceous materials, polysaccharides, such as pectin, for example, and mixtures thereof. In another aspect of the invention there is also dispersed throughout the matrix a combining agent, such as other polysaccharides or proteinaceous materials, which are capable of absorbing, and adsorbing, substances present in biological fluids.

Microparticles are also useful in chemical reactions in the present invention. For example, microparticles having a water insoluble enzyme matrix can be utilized to catalyze certain chemical reactions. Despite being crosslinked and rendered water insoluble during preparation of the microparticles, the proteinaceous or polysaccharide material, whether present as matrix material or combining agent, retains sufficient activity to absorb substances in biological fluids. Moreover, the microparticles retain their permeability despite being crosslinked. Thus, the particles increase in size, e.g., as well as allowing biological fluids to penetrate them.

The drug matrix combination of the invention can also be provided in liposomes, or,

comprise liposomes. Controlled release liposomal liquid pharmaceutical formulations for injection or oral administration are described in Suzuki *et al.*, U.S. Patent No. 4,016,100. Liposomal applications for oral drug delivery of lyophilized liposome/peptide drug mixture filled into intestine capsules have also been suggested as in Horokoshi *et al.*, U.S. Patent No. 4,348,384. As already indicated in some instances the drug will be encapsulated particularly in liposomes. Liposomes are prepared from a variety of lamellar forming lipids including phospholipids, for example, phosphatidyl choline, phosphatidyl ethanolamine, gangliosides and sphingomyelin, steroids and cholesterol. Usually the weight of the lipids in relation to the weight of drug will range from 1 to 5 liters of entrapped drug per mole of amphipathic lipid. In addition the drugs can be employed encapsulated in liposomes or other controlled rate release compositions which are included in the matrix compositions so as to provide for separate and distinct rates of release for the drug. In this way, multiphasic compositions can be prepared so as to provide for sustained release of the drug or drugs over long periods of time. Formation of liposomes with inclusion of various materials is described in Papahadjopoulos (1978) Annals of the N. Y. Academy of Science *308*: Gregoriadis and Allison (1980) Liposomes and Biological Systems. John Wiley & Sons: Leserman *et al.*, *Nature 293*:226-228 (1981).

The formulations and method of the present invention are considered to be generally useful for the delivery of a desired agent in which the colonic contents or colonic tissue metabolize the desired agent to a more desired form, for example, a more active metabolite as in the case of sulindac. Such a more desired form is thus synthesized in a preferential manner for providing a locally higher concentration by targeted delivery for local treatment of the colon, than when the drug is administered systemically or orally in a conventional manner. Optionally and preferably, these methods and compositions are useful for the administration of orally administered drugs or chemical agents that are processed to active metabolites in the colonic environment for a subject who suffers from impaired liver function. This impaired function impairs normal hepatic metabolism of drugs to active metabolites. Metabolism in the colon can serve an alternative for metabolism in the liver for such drugs in these subjects.

Therefore, prodrugs, either alone or in combination with other prodrugs or drugs, may be used in the practice of this invention. Many prodrugs have been proposed for specific colonic delivery wherein the active moiety is bound to a sugar or a polymer (carrier molecule) which renders the active molecule inactive, such as glucuronide for example. Upon colon arrival, the special chemistry of the colon contents or the colon microflora release the drug from its carrier molecule. Some such prodrugs are partially or significantly absorbed through the GI tract

thereby preventing some of the drug from arriving in the colon to be metabolized to the active drug. Even such prodrugs that are not absorbed are diluted by intestinal fluids making the concentration of the obtained metabolite lower than that obtainable by delivering the same prodrug with the delivery systems of this invention. Delivery of the prodrug preferentially to the colon will result in higher concentrations of the active moiety than otherwise attainable. This should be useful for local treatment of disease and to assist in concentration gradient driven drug absorption.

As noted previously, a particularly preferred example of such a drug, which is locally administered to the colon for the purpose of promoting metabolism of the drug to a more active metabolite, is sulindac, particularly for the treatment of colorectal polyps. Such local treatment enhances the amount of sulindac which is converted into the more active metabolite, sulindac sulfide, when compared to the amount that is converted into sulindac's less active metabolite, sulindac sulfone, by minimizing the amount of sulindac that is absorbed into the bloodstream and by maximizing the amount of sulindac that is delivered to the colon - at which location the sulindac is preferentially metabolized into sulindac sulfide by the colonic environment and absorbed therefrom. Thus, the present invention also encompasses a method for the administration of sulindac to a patient in need of the same wherein the majority, if not all, of the dose of sulindac that is administered to such a patient is delivered to the colon of the patient.

The sulindac can be provided alone or in combination with other therapeutic agents and at doses and times known in the art. Preferred doses are 50-500 mg/day in single or divided doses, most preferably 150-300 mg/day in single or divided doses. Any delivery system that will deliver the sulindac to the colon can be used. Sulindac delivered directly to the colon is converted into the active metabolite sulindac sulfide, which, in addition to creating a relatively high local colonic concentration of sulindac sulfide, can be absorbed into the bloodstream from the colon. Sulindac delivered preferentially to the colon will result in highly significant concentrations of the potent COX-2 inhibitor metabolite in the lumenal contents of the colon and in the colon wall, allowing anti-inflammatory and anti-neoplastic activity not otherwise attainable at the lower concentrations formed through systemic delivery. Use of this method results in an enhanced concentration of sulindac sulfide and in a more efficacious treatment for the prevention or regression of colon polyps and for the prevention or treatment of colon cancer.

With regard to specific therapeutic agents which may be administered with the formulations, delivery system and methods of the present invention, particularly preferred examples of such agents include, but are not limited to, an NSAID (non-steroidal anti-

inflammatory drug); a COX-2 inhibitor, whether as the desired agent itself or as the metabolite of such an agent; anti-cancer drugs; steroidal drugs; 5HT 3 antagonists; 5HT 4 antagonists; 5HT 4 agonists; and the like.

In a further embodiment, the methods and formulations of the present invention are used to deliver an anti-inflammatory drug, such as an NSAID (non-steroidal anti-inflammatory drug), locally to the colon of a patient in need of the same, so that such anti-inflammatory drug can exert its effects directly on the colon. Such method obviates concerns about systemic overdosing of the anti-inflammatory drug. In addition, such method allows a study of the mechanism of action of the anti-inflammatory drug since it provides a mechanism of assessing the local effects of the drug.

An example of such an anti-inflammatory drug which is not an NSAID is 5-ASA (5-aminosalicylic acid), which acts locally and has low systemic absorption. 5-ASA may optionally be administered directly in the formulation of the present invention. Alternatively, 5-ASA may be administered in a prodrug form in the formulation of the present invention, for example as sulfasalazine or balsalazide. Sulfasalazine is itself an NSAID, although its active metabolite, 5-ASA, is not. Such a prodrug form of 5-ASA would then be converted to the active metabolite in the colon, as described in greater detail above.

Examples of NSAIDs that may be provided in the formulation and methods of the invention include, for example, the carboxylic acid NSAIDs and the pyrazolone butazone propazone NSAIDs. Examples of the carboxylic acid NSAIDs include such as anthranilic acids, aspirin (5-acetylsalicylic acid), azodisal sodium, carboheterocyclic acids, carprofen, diclophenac, fenbufen, fenclofenac, fenoprofen, flufenamic acid, flurbiprofen, fluprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, lonazolac, loxoprofen, meclofenamic acid, mefanamic acid, naproxen, phenylacetic acids, proprionic acids, salicylic acids, salazosulfapyridine, sulindac, sulindac sulfide, sulindac sulfone, and tolmetin. Examples of the pyrazolone butazone propazone NSAIDs include meloxicam, oxicams, piroxicam (for example, feldene or piroxicam beta cyclodextran), and tenoxicam. Other NSAIDs useful in the practice of the invention include etodolac and oxaprozin. Other suitable embodiments useful in the practice of the invention are combinations of an NSAID with other agents, for example, as provided by Arthrotec (a combination of diclofenac sodium and misoprostol, a synthetic prostaglandin, Searle). Combinations of non-steroid anti-inflammatory drugs such as sodium diclofenac, sulindac, endomethycin, ibuprofen, ketoprofen, diflunisal piroxicam, naproxicam, naproxen, flurbiprofen, sodium tolmetin, any other agent having NSAID activity, drugs of peptidic nature and

cyclooxygenase inhibitors may be present in the composition of the present invention.

Therapeutic agents suitable for incorporation into dosage forms of the present invention are those for which release in the colon or delayed release is therapeutically advantageous. These include therapeutic agents useful for topical treatment of diseases of the colon such as polyps, carcinomas, and infection in which systemic absorption of a therapeutic agent is neither required nor desired. These include non-steroidal anti-inflammatory drugs such as 5-amino salicylic acid, immunosuppressants such as cyclosporine A, and chemotherapeutics such as methotrexate for treatment of carcinomas.

In another embodiment, chemotherapeutic agents are administered contemporaneously with an enzyme cyclooxygenase inhibitor. Examples of inhibitors include nonsteroidal anti-inflammatory drugs (NSAID), wherein the addition of an enzyme cyclooxygenase inhibitor to the treatment enhances the antitumor effects of the chemotherapeutic agent by blocking metabolism of arachidonic acid to inhibit cell regulation processes. Examples of inhibitors include nonsteroidal anti-inflammatory drugs such as minocycline hydrochloride (Nino), Diflunisal (Diflun) or Sulindac (Sulin).

In a preferred embodiment, one method to avoid gastropathy problems that occur with NSAIDs is the combination of the NSAID, where possible, with a gastric mucosal barrier protector such as the prostaglandin E2 agonist, misoprostol. Other NSAIDs that are especially useful in the practice of the invention include those that selectively inhibit COX-2 more than they do COX-1. Meloxicam is a first generation NSAID which is selective COX-2 inhibitor and relatively more gastric friendly. Another NSAID useful in the practice of the invention is nabumetone. Another medication useful in the practice of the invention is acetaminophen.

Examples of suitable anti-cancer drugs include, but are not limited to, chlorambucil , methotrexate, irinotecan, sulindac and melphelan. Sulindac is currently in clinical trials as a potential anti-cancer therapeutic agent.

Irinotecan ([1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano [3',4':6,7] indolizino [1,2-b] quinolin-9-yl ester) is disclosed in U.S. Patent No. 4,64,463, and is particularly preferred for administration with the formulation of the present invention, since it forms an active metabolite in the colon, and has both local and systemic effects against cancers of the colon. The systemic effects of irinotecan are particularly useful for the treatment of colon cancers which have metastasized outside of the colon. Thus, irinotecan is useful for the two-stage method of treatment according to the present invention, in which a drug has both local effects at the colon, and systemic effects outside the colon, for a

colonic disease condition such as cancer.

Examples of suitable steroids include systemically administered steroids such as hydrocortisone, prednisone, prednisolone, dexamethasone, methylprednisolone, betamethasone, cortisone acetate, triamcinolone, fluoromethalone, desoximetasone, fludrocortisone acetate, and cortisone; and locally administered steroids such as budesonide, prednisolone sodium metasulphobenzoate, tixocortol pivalate, prednisolone sodium phosphate, flunisolide, triamcinolone acetonide, flucinonide, desonide, beclomethasone dipropionate, fluticasone propionate, and hydrocortisone acetate. Glucocorticoids have been used in IBD (inflammatory bowel disease) for many years and are the mainstay of treatment in active ulcerative colitis. Recent developments suggest that absorption may not be necessary for treating IBD. In addition, colonic delivery may potentially reduce the systemic side effects, especially with long term, chronic use. By delivering the drug topically to the site of action (inflamed mucosa) smaller doses can theoretically be administered and as a result a lower systemic exposure is possible.

Other suitable drugs for the treatment of IBD include immunosuppressants such as microphenylate, which are also useful for administration with the formulation of the present invention.

Other suitable drugs which can be locally administered to the colon for local treatment include, but are not limited to, 5HT 3 antagonists, 5HT 4 antagonists and 5HT 4 agonists.

A wide variety of chemotherapeutic drugs may be employed individually or in combination. The drugs may be embedded in, or bound to, the matrix. Binding may be through the formation of complexes, salt formation, coordination complexes or the like. The drugs may be used individually or in combination depending upon the nature of the drug, the tumor and whether cooperative action is pharmacologically indicated. The drug composition can be provided in a form that is modified, for example. In a preferred embodiment, a drug is modified to provide for bonds that allow enzymatic cleavage, for example, by hydrolysis.

With regard to agents such as anti-cancer drugs, an optional but further preferred embodiment of a method according to the present invention is possible, in which the drug is administered locally to the colon for local treatment in a first stage. In a second stage, the drug is also absorbed systemically for systemic treatment of the colonic disease state. Such a method is particularly preferred for the treatment of cancers of the colonic tissue, since if the cancerous cells have metastasized beyond the colon, the drug must also be absorbed systemically for effective treatment of the cancer. Such metastasized cells can be described as a "colonic disease condition" or a "colonic disease state", in that these cells are part of the colonic cancer and must

therefore be treated as part of the disease of the colon, regardless of their precise location in the body of the subject. Such a two-stage method of treatment is not effectively provided by the background art, since it requires both targeted delivery to the colon and systemic absorption of sufficient amounts of the drug for effective treatment of the colonic cancer.

As previously noted, irinotecan is particularly preferred for administration with the formulation of the present invention in this method, for having both local and systemic effects against cancers of the colon. The systemic effects of irinotecan are particularly useful for the treatment of colon cancers which have metastasized outside of the colon. Thus, irinotecan is useful for the two-stage method of treatment according to the present invention, in which a drug has both local effects at the colon, and systemic effects outside the colon, for a colonic disease condition such as cancer.

Colonic diseases for which the formulations of the present invention may be effectively used for the local administration of therapeutic agents to the colon include, but are not limited to, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), Crohn's disease, polyps, ulcerative colitis, precancerous and cancerous lesions, constipation, dysfunctions of colonic motility, local spasmolytic action, ulceration of the mucosa, diarrhea, carcinomas, cysts, infectious disorders, and parasitic disorders.

Types of polyp conditions or syndromes that would benefit by treatment according to the invention include adenomatous colonic polyps (especially of the large bowel, the precursor lesions for the vast majority of colorectal cancers), common sporadic polyps, familial adenomatous polyposis (FAP), polyposis syndromes, Gardner's Syndrome with colon polyposis, and colorectal carcinoma. The difference between common sporadic polyps and polyposis syndromes is dramatic. Common sporadic polyp cases are characterized by relatively few polyps, each of which can usually be removed leaving the colon intact. By contrast, polyposis syndrome cases can be characterized by many (hundreds or more) of polyps literally covering the colon in some cases, making safe removal of the polyps impossible short of surgical removal of the colon.

Accordingly, a subject in need of treatment with a desired drug, especially when it is desired to target the desired drug to the site of such subject's colon, may conveniently obtain such treatment by orally ingesting the composition of the invention. Alternatively, if desired, the composition of the invention may be provided in suppository form. Compositions for rectal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax. The composition of the

invention may also be administered directly into the colon of such patient by the physician at the time of colonoscopy, for example.

Subjects in need of treatment according to the method of the invention are especially those who are at risk for development of polyps and/or colon cancer and most especially high risk patients as previously defined.

For any of the colonic diseases and colonic disease states as previously described, the formulations and colonic delivery system of the present invention contains the therapeutic agent, alone or in combination with other therapeutic agents, and contains the agents in any dosage level necessary to achieve a therapeutic benefit. The dosage level used depends upon the disease to be treated. Further, the level of one therapeutic agent may be present at a level different from the level of the other therapeutic agents present and each agent may be released at different levels and at different intervals than the other therapeutic agents present. The agent can be adjusted such that it is administered for, for example, a desired length of time which gives the desired therapeutic results. The colonic delivery system of the invention that contains one or more desired therapeutic agents can be administered sporadically only when as needed or for extended periods of time, such as weeks, months or years, as desired to achieve a therapeutically beneficial result.

The actual dosage levels of active ingredients in the compositions of the invention may be varied so as to obtain an amount of active ingredient effective to achieve polyp-eliminating activity in accordance with the desired method of administration. The selected dosage level depends upon the nature of the active compound administered, the route of administration, the desired duration of treatment, and other factors, such as, for example, the age of the patient. If desired, the daily dose may be divided into multiple doses for administration, for example, two, three, or four times a day. The colonic delivery system contains the therapeutic agent, alone or in combination with other therapeutic agents, and may be administered before diagnosis and for diagnostic or prophylactic purposes.

The amount of drug can vary as desired for efficacious delivery of the desired drug and in consideration of the patient's age, sex, physical condition, disease, and other medical criteria. In addition, the amount of drug delivered by the system of the invention will depend upon the relative efficacy of the drug. The amount of specific drug necessary for efficacious results in the delivery system and methods of the invention may be determined according to techniques known in the art. For example, recommended dosages such as known in the art *(for example, see the Physicians' Desk Reference*, 1991 (E.R. Barnhart, publisher) *The Merck Index*, 10th Edition

Merck & Co., New Jersey, and *The Pharmacological Basis of Therapeutics*, 8th edition, A.G. Goodman, *et al.*, eds., Pergamon Press, New York), provide a basis upon which to estimate the amount of a drug which has been previously been required to provide an efficacious level of activity. Especially, amounts of a desired drug that have previously been administered by suppository formulations, and the known characteristics of such drug when administered by suppository, are useful in this regard. Since the delivery system of the invention does not depend upon systemic (blood) delivery of the drug to the colon, it may be expected that efficacious levels of colon drugs that must be administered to a patient systemically will be higher than efficacious levels of such drugs when delivered directly to the colon. Furthermore, it is expected that through colonic delivery, levels of the drug concentration at the site of action, and levels of active metabolites at the site of action will be higher than those attainable through systemic delivery.

It should be noted that the nature, particle size, and weight percentage, of the hydrophilic non-water-soluble particulate matter and the overall coating thickness of the delivery system coating can be varied to fine-tune the delivery to a desired site, or to adjust for a certain physiological condition of the patient. Making the insoluble particles relatively more hydrophilic or increasing their weight percent in the coating, or making their average particle size smaller for a given weight percent or making the coating thinner, all tend to promote a quicker release of the drug from the delivery system. These factors can each be altered and controlled independently of the others. The ratio of the calcium pectinate to the low methoxy pectin can also be optimized to give the best delivery profile in the colon. Increasing calcium pectinate lowers the solubility of the matrix, thus slowing erosion, while increasing pectin gives a stronger gel, thus slowing diffusion of a soluble drug from the matrix.

Tablets and capsules may be prepared and tested by techniques well known in the art, for example, as described in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, 16th edition, 1980, and especially in chapter 89, the pharmaceutical preparation and manufacture of "Tablets, Capsules and Pills." In all embodiments, if desired, more than one drug may be supplied to the patient in the same matrix. Good results have been obtained by the combined administration of, for examples, sulindac, tamoxifen and vitamin C; tamoxifen and sulindac; warfarin and vitamin K1; and steroids and tamoxifen. These are cited in the following references: Waddell, W.R., Gerner, R.E., Reich, M.P., *Nonsteroid Anti-inflammatory Drugs and Tamoxifen for Desired Tumors and Carcinoma of the Stomach, J. Surg. Oncol. 22*:197-211 (1983); Tsukada, K., Church, J.M., Jagelman, D.G., *et al., Noncytoxic Drug Therapy for Intra Abdominal Desmoid Tumor in Patients with Familial Adenomatous Polyposis Dis Colon*

Rectum 35:29-33 (1992). Other chemical substances which may have use in the practice in the invention are vitamin A, vitamin C, vitamin D, vitamin E, multivitamin compositions, calcium and mineral supplementation. Other chemical compounds having use in the practice of the invention are carotenoids, anti-oxidant vitamins, folic acid and flavenoids. In addition, the matrix can be used to release therapeutic levels of dietary supplements such as metals, trace elements, etc., to combat certain conditions including anemia, for example.

In the controlled-release systems currently known in the art, drugs are released by diffusion mechanisms during transit of the drug-containing composition throughout the gastrointestinal tract. The drug is absorbed and metabolized in the gut wall or in the liver. Only a small portion of the drug reaches the colon and that portion is in a diluted state having been diluted by intestinal fluids. Less of the drug is available for treatment and less is available for the advantageous metabolism to a more active moiety. According to the present invention this problem is overcome by incorporating the drug in a suitable colonic delivery matrix or, if the drug is contained in a core, coating such core with a suitable coating that can deliver the drug preferentially to the colon. Thus, in such systems, most if not the entire dose of the drug is delivered to the colon for treatment of the colon polyps, and most or the entire dose is available for advantageous metabolism to a highly active species.

In an initial study of ten healthy volunteers, in which placebo calcium pectinate matrix tablets were administered, the transit time and disintegration of the radiolabeled formulation was followed by gamma scintigraphy. It was demonstrated that the tablets arrived in the colon essentially intact and that complete tablet disintegration occurred in the colon in all subjects (Adkin, D.A., *et al., Pharmaceutical Research 14.1*:103-107 (1997), incorporated herein by reference.

Other suitable embodiments will be known to those of skill in the art. A useful formulation will be suitable for enteric administration, will contain a drug targeted for release in the colon, and will further contain either a saccharide containing polymer matrix and/or a particulate containing coating according to the invention. The formulation will be designed so as to allow protection of the drug from stomach and intestinal enzymes, but permitting release of the drug in the colon either by biodegradation of the matrix or by drug diffusion through the particulate channels in the coating.

The delivery system and methods of the invention are not limited to administration to humans and are especially useful for veterinary administration of drugs to any animal, including pets such as dogs, cats, horses, fish and birds, zoo animals, wild animal control and treatment

and agriculturally important animals of the food and dairy industry such as cattle, milk cows, swine and poultry.

The following examples further describe the materials and methods used in carrying out the invention. The examples are not intended to limit the invention in any manner.

5

Example 1

Cross-Over Pilot Colonic Delivery Study

10 A cross-over pilot colonic delivery study involving two NSAID (diclofenac sodium) colonic drug delivery tablet formulations with different coating levels and either a commercial slow release (SR) diclofenac sodium or a diclofenac sodium - matrix CDS without a CDS coating as reference was performed in 12 healthy volunteers. The objective of the study was to provide a comparison of the local colonic delivery of two coated sustained release (SR) colonic 15 delivery system (CDS) formulations containing 100 mg sodium diclofenac to a matrix CDS formulation and to a commercial diclofenac slow release formulation (100 mg) as a positive control.

To this end, sodium diclofenac was formulated into a matrix tablet of 9 mm diameter which contained 100 mg diclofenac sodium, 80 mg calcium pectinate, 50 mg low methoxy 20 pectin, 70 mg hydroxypropylmethylcellulose, and 0.6 mg magnesium stearate. This tablet was coated with the CDS particulate-containing coating where the hydrophobic insoluble polymer was Eudragit E and the hydrophilic, water-insoluble particles were calcium pectinate of particle size <150 microns at 70% by weight. Treatment A was coated with about a 35 micron thick CDS coating and subsequently with a standard enteric coating based on Eudragit L. Treatment B 25 was coated with about a 60 micron thick CDS coating and subsequently with a standard enteric coating. Treatment D was not coated with the CDS particulate containing coating but was coated with the same standard enteric coating as the other two treatments. Treatment C was a commercially available slow release diclofenac formulation that made no claims of colonic delivery. It was administered for purposes of comparison.

30 The trial methodology was an open label, blinded to the analyst, three-way randomized cross-over design (Latin square) with twelve (12) volunteers. The twelve volunteers were divided into two groups. One group received the following three treatments:

A. Diclofenac sodium CDS with 35 micron CDS coating + enteric coat;

B. Diclofenac sodium CDS with 60 micron CDS coating + enteric coat;

C. Commercial diclofenac sodium SR tablet.

The second group received the following three treatments:

A. Diclofenac sodium CDS with 35 micron CDS coating + enteric coat;

B. Diclofenac sodium CDS with 60 micron CDS coating + enteric coat;

D. Diclofenac sodium CDS + enteric coat.

Each volunteer received one of the treatments at baseline and the others with a washout phase of at least one week between the drug administrations. Venous blood samples were taken before dosing and at predetermined intervals between 4 and 36 hours after dosing. The concentration of diclofenac was determined in the blood samples using a validated procedure based on extraction and HPLC analysis. Colonic delivery is shown by the time profile of diclofenac in the blood. Adverse effects were monitored at each visit.

Pharmacokinetic Results

The plasma concentration curves of diclofenac showed more than one peak in several instances. C_{max} and t_{max} relate to the highest observed concentration regardless of other peaks present in the graph. The t_{max} of the averaged data for Treatments A and B was 12 hours and 16 hours respectively. Table 1 collects the individual data for C_{max} and t_{max} for the twelve volunteers.

Table 1: Individual Data for C_{max} and t_{max}

	C_{max} (ng/ml)	t_{max} (hours)	C_{max} (ng/ml)	t_{max} (hours)	C_{max} (ng/ml)	t_{max} (hours)	C_{max} (ng/ml)	t_{max} (hours)
Treatment	A	A	B	B	C	C	D	D
volunteer								
1	144	16	192	28	395	6		
2	245	12	228	14	123	6		
3	321	12	328	14	573	4		
4	179	18	105	14	222	6		
5	232	8	257	18	223	6		
6	213	14	170	20				
7			96	36				
8	426	12	452	12			151	16
9	482	14						
10	226	16	416	16			290	10
11	176	18	274	24			186	18

	C_{max} (ng/ml)	t_{max} (hours)	C_{max} (ng/ml)	t_{max} (hours)	C_{max} (ng/ml)	t_{max} (hours)	C_{max} (ng/ml)	t_{max} (hours)
Treatment	A	A	B	B	C	C	D	D
12	383	16	277	24			212	22
Mean	275.2	14.2	254.1	20.0	307.2	5.6	209.8	16.5
STDDEV	111.6	3.0	114.3	7.4	177.9	0.9	59.1	5.0
Median	232	14	257	18	223	6	199	17
Maximum	482	18	452	36	573	6	290	22
Minimum	144	8	96	12	123	4	151	10

The mean t_{max} ± Standard Deviation for the individual data for Treatments A and B was 14.2±3.0 hours (n=11) and 20.0±7.4 hours (n=11) with ranges (maximum-minimum) of 18-8 hours and 36-12 hours respectively. The variability in t_{max} was greater for Treatment B than for Treatment A. indicating a possible dependence of the variability on the value of t_{tmax}. The positive control, Treatment C, delivered its maximum concentration at an earlier time. The t_{max} for the averaged data was six hours and the mean t_{max} for the individual data was 5.6±0.9 hours (n=5) with the data ranging from 6-4 hours. The mean t_{max} for the individual data for Treatment D was 16.5±5.0 hours (n=4) with a range 22-10 hours. The t_{max} data clearly shows a delayed delivery of the Diclofenac from Treatments A and B as compared to Treatment C. Treatment D shows both early and delayed drug delivery.

The mean C_{max} for Treatment A was 275.2±111.6 ng/ml (n=11) with the values ranging from 482-144 ng/ml, for Treatment B the values were 254.1±114.3 ng/ml (n=11) with the values ranging from 452-96 ng/ml, for Treatment C the mean C_{max} was 307.2±177.9 (n=5) with the values ranging from 573-123 ng/ml. and for Treatment D the mean C_{max} was 209.8±59.1 ng/ml (n=4) with a data range of 290-151 mg/ml. All three CDS formulations had lower mean

maximal concentrations than the commercial SR formulation.

The results of the extent of absorption to six hours (AUC_{0-6}/AUC_{0-36}) for the individual profiles are collected in Table 2. AUC is the area under the curve for the concentration versus time graph. AUC_{0-36} is the area under the curve for the entire measurement period of 36 hours and represents the full extent of drug absorption. AUC_{0-6} represents the area under the same curve from zero to six hours and represents the diclofenac sodium found in the blood in the first six hours. The quotient of these numbers represents the fraction of the drug absorbed that is absorbed in the first six hours. One can see that the mean value for treatments A and B are 0.08±0.03 and 0.05±0.05 with ranges of 0.16-0.03 and 0.13-0.00 respectively while for Treatment C the mean value is 0.59±0.13 with a range of 0.69-0.37. Treatment D gave a mean value of 0.22 ± 0.09 with a range of values of 0.33-012. The extent of absorption to six hours is clearly much lower for Treatments A and B, of intermediate nature for Treatment D and is high for Treatment C.

Table 2. Extent of Absorption to Six Hours

Summary for AUC_{0-6}/AUC_{0-36}				
Treatment	A	B	C	D
vol#				
1	0.08	0.06	0.37	
2	0.16	0.11	0.66	
3	0.05	0.00	0.61	
4	0.07	0.00	0.64	
5	0.10	0.06	0.69	
6	0.09	0.00		
7		0.13		
8	0.08	0.08		0.12
9	0.06			
10	0.10	0.05		0.33
11	0.06	0.00		0.20
12	0.03	0.02		0.22

Mean	0.08	0.05	0.59	0.22
STDDEV	0.034	0.047	0.129	0.087
MAX	0.16	0.13	0.69	0.33
MIN	0.03	0.00	0.37	0.12

The results for the calculation of the AUC_{0-36} for the individual data for all the volunteers are collected in Table 3.

Table 3. Summary of Individual AUC Data

	PPL#1	PPL#2	Commercial SR	PPL-UC
Treatment	A	B	C	D
volunteer	AUC_{0-36} (h)(ng/ml)	AUC_{0-36} (h)(ng/ml)	AUC_{0-36} (h)(ng/ml)	AUC_{0-36} (h)(ng/ml)
1	1828	1418	1060	
2	1760	1360	707	
3	2878	2696	3526	
4	1682	1395	1031	
5	1822	1682	1082	
6	1821	1592		
7		1043		
8	2578	2126		1757
9	2421			
10	2737	2361		2639
11	2294	2563		2518

	PPL#1	PPL#2	Commercial SR	PPL-UC
12	2329	2552		2576
Mean	2192.7	1889.8	1481.2	2372.5
STDDEV	427.8	584.5	1153.3	413.3
Median	2294	1682	1060	2547
Maximum	2878	2696	3526	2639
Minimum	1682	1043	707	1757

The mean AUC_{0-36} for the individual data for Treatments A, B. C and D were 2193±428, 1890±585. 1481±1153 and 2373±413 (h)(ng/ml) showing that the CDS formulations were better than. or at least as good as. the positive control in this respect. The value for the positive control might be artificially low because a two hour time point was not taken. There is no difference seen between the

AUC_{0-36} values for the three CDS formulations. The values for the AUC_{0-36} for the averaged values are identical to the average values for the individual data.

Diclofenac was quantifiable (defined as a mean concentration above the lowest quantifiable concentration of the analysis - 10 ng/liter) for Treatment A from 4 hours to 30 hours, for Treatment B from 4 hours to 36 hours, for Treatment D from 4 hours to 30 hours while for Treatment C from 4 hours to 12 hours. The individual data for the number of quantifiable results for each formulation as a function of time are collected in Table 4.

Table 4

Time (hours)	Treatment A Q/T[1]	Treatment B Q/T[1]	Treatment C Q/T[1]	Treatment D Q/T[1]
0	0/11	0/11	0/5	0/4
4	10/11	6/11	4/5	4/4
6	11/11	7/11	5/5	4/4
8	11/11	8/11	5/5	4/4
10	11/11	7/11	5/5	4/4
12	11/11	9/11	4/5	4/4
14	11/11	8/11	1/5	4/4
16	11/11	8/11	1/5	4/4
18	11/11	8/11	1/5	4/4
20	10/11	11/11	1/5	3/4
22	11/11	11/11	1/5	3/4
24	11/11	10/11	1/5	4/4
26	10/11	8/11	1/5	4/4

Time (hours)	Treatment A Q/T[1]	Treatment B Q/T[1]	Treatment C Q/T[1]	Treatment D Q/T[1]
28	7/11	9/11	0/5	2/4
30	7/11	8/11	0/5	2/4
36	4/11	7/11	0/5	1/4

[1]Q/T is number quantifiable/total number of measurements.

The individual data corroborate that the CDS formulations give quantifiable concentrations of diclofenac for times that the formulation is expected to be in the colon, compared to Treatment C which was quantifiable up to only 12 hours in four of the five volunteers.

Discussion

The coated CDS formulations, Treatments A and B, showed their maximal concentrations at times that clearly correspond to colonic drug absorption. The residence time in the stomach for the fasted state is up to two hours and the average transit time in the small intestine is 3-5 hours (Davis, S., *et al.*, *Gut* 27:886 (1986)) so that a t_{max} greater than six hours is indicative of colonic absorption. The values of 14 hours for the coated CDS Treatment A, 20 hours for the coated CDS Treatment B, and 16 hours for the non coated CDS Treatment D, are indicative of the maximal drug delivery taking place in the colon. The positive control, Treatment C, delivered its maximum concentration at a time that corresponds to small intestinal delivery.

The area under the concentration versus time curve to a given time represents the amount of the drug absorbed up to that time point. The ratio of that area to the total area gives a representation of the percentage of the total drug absorbed that was absorbed up to that point. The percent extent of absorption in the first six hours (defined as (100) (AUC_{0-6}/AUC_{0-36}) where AUC_{0-6} is the area under the concentration vs. time curve from 0 to 6 hours and AUC_{0-36} is the

area under the entire curve in our experiment) from the averaged data was 8% for Treatment A, 4% for Treatment B, 59% for Treatment C and 23% for Treatment D indicating essentially colonic delivery for Treatments A and B, mostly colonic delivery for treatment D and mostly small intestine delivery for Treatment C.

These values again clearly indicate that Treatments A and B deliver the drug essentially in the colon while Treatment C delivers the majority of its drug before colonic arrival. The non-coated CDS, while delivering it maximal drug concentration through the colon, delivered some of the drug before arrival in the colon.

Blood C_{max} levels were lower for the colonic delivery formulations than for the commercial SR product. It is expected that colonic delivery thus promotes a lower incidence of systemically caused side effects.

Safety Evaluation

Twelve subjects were evaluated for safety. No serious adverse events occurred in the course of the study. Seven subjects showed mild adverse events, not all of which are drug related.

Conclusions

The new colonic delivery systems resulted in diclofenac concentrations that were quantifiable for 24 to 28 hours, indicating sustained colonic delivery of the drug. The CDS with the coatings gave low drug release in the first six hours, indicating effective protection of a soluble drug before colonic arrival. It is therefore concluded that the CDS is an effective and well tolerated NSAID drug delivery system to the large intestine.

Example 2

A Pharmacokinetic Study of Sulindac and Its Metabolites

A crossover pharmacokinetic study involving two dosing levels of CDS-sulindac with one dose of commercially available sulindac as a reference was performed. The objective of the study was to compare the pharmacokinetic profile of sulindac delivered to the colon to sulindac

delivered to the upper GI tract (stomach and small intestine) and to compare the concentrations and relative formation of the two major metabolites of sulindac, sulindac sulfide and sulindac sulfone.

To this end sulindac was formulated into a CDS 9 mm tablet containing 150 mg sulindac, 77.5 mg calcium pectinate, 77.5 mg low methoxy pectin, 45 mg hydroxypropylmethylcellulose, and 1.8 mg magnesium stearate. This tablet was coated with about a 30 micron thick CDS coating consisting of 30% Eudragit E and 70% calcium pectinate of particle size <150 micron and further coated with an enteric coat based on Eudragit L. Commercially available 150 mg tablets of sulindac were used as a reference material.

The trial methodology was an open label, blinded to the analyst, three-way crossover design with 18 volunteers. Each of the volunteers received all three treatments in random order, one at baseline and the other two at intervals of one week for drug washout. The three treatments were:

A. One tablet sulindac CDS

B. Two tablets of sulindac CDS

C. Two tablets of commercial sulindac

Venous blood samples were taken before dosing and at predetermined time intervals from 0.5 to 96 hours after dosing. The concentration of sulindac was determined in the blood samples using a validated sample preparation procedure and an HPLC analysis. The concentrations of sulindac and its metabolites sulindac sulfide and sulindac sulfone were monitored. Colonic delivery is shown by the time profile of sulindac in the blood. Differences between the hepatic metabolism of sulindac in the blood and colonic metabolism of sulindac are evaluated by monitoring the concentrations of the metabolites and the parent drug as a function of time.

Results - sulindac

The concentration profiles of sulindac in plasma for the two CDS treatments were similar but quite different from that of the commercial sulindac. C_{max} and t_{max} relate to the highest observed concentration. The averaged data for sulindac in all three treatments are shown in Figure 1. The t_{max} of the averaged data for treatments A and B was 6 hours and 10 hours respectively. The t_{max} for the averaged data for treatment C was 3 hours. The individual data for

t_{max} and C_{max} for the 18 volunteers is provided in Table 5. The mean t_{max} ± standard deviation for the three treatments was 8.3 ±5.5, 7.00 ±2.80, and 1.66 ±0.86 hours respectively with ranges (maximum - minimum) of 28-4, 12-4, and 4-0.5 hours respectively. When compared to treatment C, the two CDS tablets showed delayed delivery of the sulindac.

TABLE 5: C_{max} and t_{max} for Sulindac

Volunteer No.	Treatment A		Treatment B		Treatment C	
	C_{max} (mg/ml)	t_{max} (hours)	C_{max} (mg/ml)	t_{max} (hours)	C_{max} (mg/ml)	t_{max} (hours)
1	0.26	8	0.77	10	6.26	2
2	0.43	6	2.70	10	5.77	1
3	0.17	10	0.24	4	7.46	1
4	0.14	6	0.45	6	8.75	1
5	0.25	10	0.45	12	8.24	2
6					9.59	2
7	0.07	6	0.2	4	4.57	2
8	0.85	6	1.15	4	9.75	2
9	0.11	4	0.18	10	5.35	1

10	0.14	4	0.48	8	9.76	2
11	0.53	8	0.36	8	3.77	4
12	0.18	6	0.38	4	6.57	0.5
13						
14	0.24	28	1.0	8	9.08	2
15					9.52	1
16	0.23	10	1.09	8	8.07	2
17					9.70	1
18	0.17	6	0.66	4	9.53	4
Mean	0.27	8.3	0.72	7	7.75	1.7
Standard	0.21	5.5	0.65	2.8	1.99	0.8
Maximum	0.85	28	2.70	12	9.76	4
Minimum	0.07	4	0.18	4	3.77	0.5

The mean C_{max} for treatment A was 0.27 ±0.21 (mg/ml) with the values ranging from 0.85-0.07, for treatment B was 0.72 ±0.65 (mg/ml) with the values ranging from 2.7- 0.18, while for treatment C the value was 7.76 ±1.99 (mg/ml) with the values ranging from 9.76-3.77. The C_{max} of sulindac was considerably lower for the CDS formulations.

The area under the curve of concentration of sulindac vs. time (AUC) for all 18

volunteers is given in Table 6. The mean AUC from zero to 96 hours (AUC_{0-96}) was 3.50 ±2.50 (h)(mg/ml) with values ranging from 8.63 to 0.24 for treatment A, 8.42 ±6.37 (h)(mg/ml) with values ranging from 22.8 to 2.48 for treatment B and 25.66 ±7.52 (h)(mg/ml) with values ranging from 43.57 to 13.2. The AUC for the sulindac from the CDS formulations were considerably lower than the commercial product.

TABLE 6: AUC_{0-96} for Sulindac

Volunteer No.	Treatment A	Treatment B	Treatment C
	AUC_{0-96} (h)(mg/ml)	AUC_{0-96} (h)(mg/ml)	AUC_{0-96} (h)(mg/ml)
1	2.88	5.7	19.26
2	3.86	21.26	22.38
3	2.17	4.72	26.56
4	3.26	5.76	18.55
5	2.52	2.46	26.94
6			34.21
7	0.24	2.98	13.20
8	7.68	12.88	36.32
9	2.96	5.81	22.16

Volunteer No.	Treatment A	Treatment B	Treatment C
	AUC_{0-96} (h)(mg/ml)	AUC_{0-96} (h)(mg/ml)	AUC_{0-96} (h)(mg/ml)
10	0.46	5.36	33.00
11	4.62	4.97	16.41
12	3.61	5.89	19.73
13			
14	8.85	22.80	
15			30.05
16	3.76	10.61	24.54
17			39.43
18	3.73	5.71	27.99
Mean	3.61	8.35	25.61
Standard	2.3	6.37	7.52
Maximum	8.85	22.80	39.43
Minimum	0.24	2.46	13.20

TABLE 7: Extent of Absorption of Sulindac at Six Hours

	Total Absorption	To 6 Hours	Extent of Absorption
	AUC_{0-96}	AUC_{0-6}	AUC_{0-6}/AUC_{0-96}
Treatment A	3.6	0.35	0.10
Treatment B	8.4	0.4	0.05
Treatment C	25.6	22.2	0.87

Table 7 shows the values of AUC_{0-96} and AUC_{0-6} the averaged data for all three treatments and the ratio AUC_{0-6}/AUC_{0-96} as the extent of absorption to 6 hours. Six hours is considered the time of definite colon arrival since in fasted subjects the tablet will stay 0-2 hours in the stomach and 3 ± 1 hours in the small intestine. We see that the extent of absorption to six hours for treatment A is 10%, for treatment B is 5% while for treatment C it is 87%. As expected the extent of absorption in the first six hours is much lower for the CDS tablets than for the commercial sulindac.

Results - Sulindac sulfide and sulindac sulfone

The averaged data for the concentration of sulindac sulfide and sulindac sulfone in the blood are given in Figure 2 and Figure 3 respectively. The t_{max} and C_{max} values for the sulfide and sulfone for the individual volunteers are given in Tables 8 and 9 respectively while the AUC values are given in Tables 10 and 11 respectively.

TABLE 8: C_{max} and t_{max} for Sulindac Sulfide

Volunteer No.	Treatment A		Treatment B		Treatment C	
	C_{max} ug/ml	t_{max} hours	C_{max} ug/ml	t_{max} hours	C_{max} ug/ml	t_{max} hours
1	1.01	8	2.66	10	4.25	4
2	0.85	14	6.00	12	2.82	4
3	0.82	14	0.82	24	3.91	4
4	1.01	14	1.81	16	3.98	2
5	1.11	16	2.20	12	4.67	4
6	1.88	8	3.07	10	5.53	4
7	0.53	4	1.39	22	3.15	4
8	1.01	14	2.39	14	3.49	4
9	0.93	20	4.82	18	3.42	4
10	0.10	8	1.72	10	4.56	2
11	0.76	18	1.55	20	4.57	4
12	0.88	14	1.03	16	3.67	2

Volunteer No.	Treatment A		Treatment B		Treatment C	
	C_{max} ug/ml	t_{max} hours	C_{max} ug/ml	t_{max} hours	C_{max} ug/ml	t_{max} hours
13	1.11	10	2.09	24	4.11	4
14	2.73	12	5.64	10	6.88	4
15	0.66	8	3.88	10	6.03	2
16	1.07	10	1.98	18	5.52	4
17	0.44	24	2.24	24	3.88	4
18	0.47	20	1.46	12	3.73	2
Mean	0.97	13.1	2.59	16.7	4.34	3.45
Standard	0.58	5.2	1.53	5.32	1.06	0.91
Maximum	2.73	24	6.00	24	6.88	4.0
Minimum	0.10	4	0.82	10	2.82	2.0

TABLE 9: C_{max} and t_{max} for Sulindac Sulfone

Volunteer No.	Treatment A		Treatment B		Treatment C	
	C_{max} ug/ml	t_{max} hours	C_{max} ug/ml	t_{max} hours	C_{max} ug/ml	t_{max} hours
1	0.40	24	0.80	22	1.76	4
2	0.48	16	2.11	16	1.02	4
3	0.27	22	0.34	34	1.42	2
4	0.40	20	0.59	34	1.23	2
5	0.29	12	0.37	12	1.32	4
6	0.45	8	0.93	14	1.88	4
7	0.26	24	0.56	24	2.15	4
8	0.34	14	0.68	14	1.11	2
9	0.26	26	0.49	24	1.00	2
10	0.13	6	0.63	24	1.90	2
11	0.45	8	0.56	10	1.31	4
12	0.75	16	0.58	18	1.20	2

Volunteer No.	Treatment A		Treatment B		Treatment C	
	C_{max} ug/ml	t_{max} hours	C_{max} ug/ml	t_{max} hours	C_{max} ug/ml	t_{max} hours
13	0.47	22	0.73	24	1.73	2
14	0.24	26	0.38	10	1.11	4
15	0.29	24	0.98	16	1.51	2
16	0.79	14	1.50	14	2.21	4
17	0.38	24	0.93	26	2.98	4
18	0.28	24	0.56	36	1.83	2
Mean	0.39	18.3	0.76	20.7	1.59	3.0
Standard	0.17	6.7	0.44	8.23	0.52	1.0
Maximum	0.79	26	2.11	36	2.98	4.0
Minimum	0.13	6	0.34	10	1.00	2.0

TABLE 10: AUC_{0-96} for Sulindac Sulfide

Volunteer No.	Treatment A	Treatment B	Treatment C
	AUC_{0-96} (h)(ug/ml)	AUC_{0-96} (h)(ug/ml)	AUC_{0-96} (h)(ug/ml)
1	11.45	35.75	27.76
2	20.49	72.60	46.94
3	18.61	21.62	42.25
4	17.62	39.54	32.99
5	20.89	13.23	36.37
6	39.80	40.66	56.49
7	11.88	26.70	21.95
8	25.00	54.75	46.22
9	17.53	103.55	37.73
10	1.98	39.32	44.40
11	16.28	36.34	38.87

Volunteer No.	Treatment A	Treatment B	Treatment C
	AUC_{0-96} (h)(ug/ml)	AUC_{0-96} (h)(ug/ml)	AUC_{0-96} (h)(ug/ml)
12	14.78	27.07	29.87
13	21.92	40.08	41.97
14	80.74	161.51	139.21
15	10.17	59.64	46.48
16	13.87	35.96	34.69
17	19.53	69.70	45.66
18	13.17	25.44	35.63
Mean	20.87	50.19	44.75
Standard	16.79	35.38	24.96
Maximum	80.74	161.51	139.21
Minimum	1.98	13.23	21.95

TABLE 11: AUC_{0-96} for Sulindac Sulfone

Volunteer No.	Treatment A	Treatment B	Treatment C
	AUC_{0-95} (h)(ug/ml)	AUC_{0-95} (h)(ug/ml)	AUC_{0-95} (h)(ug/ml)
1	9.48	26.22	26.13
2	16.70	62.52	32.01
3	10.59	13.35	28.49
4	12.51	27.51	25.60
5	10.36	5.12	24.56
6	18.45	22.50	34.28
7	13.18	21.24	26.05
8	13.97	27.68	34.63
9	10.29	19.50	24.10
10	2.45	19.14	32.96
11	12.98	24.00	25.33
12	16.62	26.33	24.21

Volunteer No.	Treatment A	Treatment B	Treatment C
	AUC_{0-95} (h)(ug/ml)	AUC_{0-95} (h)(ug/ml)	AUC_{0-95} (h)(ug/ml)
13	22.19	30.91	42.36
14	10.81	18.49	24.54
15	9.74	36.51	32.52
16	23.27	39.07	39.14
17	22.19	54.22	66.55
18	11.14	26.83	35.41
Mean	13.72	27.84	32.16
Standard	5.349	13.67	10.23
Maximum	23.27	62.52	66.55
Minimum	2.45	5.12	24.10

The mean t_{max} ± standard deviation for sulindac sulfide for the three treatments were 13.1 ±5.2, 16.7 ±5.3, and 3.45 ±0.91 hours respectively with ranges (maximum - minimum) of 24-4, 24-10, and 4-2 hours respectively. The t_{max} values for the sulfone were 18.3 ±6.7, 20.7 ±8.2 and 3.01 ±1.02 with ranges of 26-6, 36-10, and 4-2 hours respectively.

The mean C_{max} for sulindac sulfide for treatment A was 0.97 ±0.58 (mg/ml) with the values ranging from 2.73-0.10, for treatment B was 2.59 ±1.53 (mg/ml) with the values ranging from 6.0-0.82, while for treatment C the value was 4.34 ±1.06 (mg/ml) with the values ranging from 6.86-2.82. The mean C_{max} values for the sulfone were 0.39 ±0.17, 0.76 ±0.44, and 1.59 ±0.52 with the values ranging from 0.79-0.13, 2.11-0.34, and 2.98-1.00 (mg/ml) respectively.

The average AUC from zero to 96 hours (AUC_{0-96}) for sulindac sulfide was 20.87 ±16.79 (h)(mg/ml) with values ranging from 80.74 to 1.98 for treatment A, 50.19 ±35.38 (h)(mg/ml) with values ranging from 161.51 to 13.23 for treatment B, and 44.75 ±24.96 (h)(mg/ml) with values ranging from 139.21 to 21.95.

The average AUC from zero to 96 hours (AUC_{0-96}) for the sulindac sulfone was 13.72 ±5.35 (h)(mg/ml) with values ranging from 23.27 to 2.45 for treatment A, 27.84 ±13.67 (h)(mg/ml) with values ranging from 62.52 to 5.12 for treatment B, and 32.15 ±10.23 (h)(mg/ml) with values ranging from 66.55 to 24.10 for treatment C.

TABLE 12: Ratio of Metabolites Sulfide/Sulfone (averaged data)

Time	Treatment A	Treatment B	Treatment C
0	-	-	-
0.5	-	-	1.43
1	-	-	2.00
2	-	-	2.43
4	1.11	0.71	2.73
6	1.36	1.43	1.83
8	1.90	3.13	1.69

Time	Treatment A	Treatment B	Treatment C
10	2.92	3.75	1.59
12	2.80	4.04	1.71
14	2.67	3.23	1.27
16	2.26	2.74	1.14
18	2.33	2.76	1.17
20	2.07	2.59	1.32
22	2.14	2.68	1.30
24	2.07	2.76	1.54
26	1.48	1.67	0.83
28	1.50	1.67	0.77
30	1.25	1.35	0.75
32	1.30	1.59	0.88
34	1.30	1.35	0.86
36	1.00	1.19	0.63
48	1.18	1.25	0.91

Time	Treatment A	Treatment B	Treatment C
72	1.25	1.43	1.25
96	-	-	0.00

Table 12 gives the ratio of the metabolites (sulfide/sulfone) as a function of time for each of the treatments. For treatment A. the ratio reaches a peak of 2.92 at 10 hours, for Treatment B 4.04 at 12 hours, while for the commercial sulindac preparation Treatment C, the ratio peaks at 2.73 at 4 hours.

The two CDS sulindac formulations. treatment A and treatment B. showed their maximal concentrations at times that correspond to colonic delivery. The residence time in the stomach in the fasted state is 0-2 hours while small intestinal transit time is 3-5 hours (Davis, S., *et. al.*, *GUT* 27:886 (1986)) so that colonic arrival is expected between a minimum of three hours and a maximum of seven hours. A t_{max} greater than 6 hours is therefore indicative of colonic absorption at the maximum. As seen in Table 5. the CDS formulations gave t_{max} of 8.29 hours and 7 hours. indicating colonic delivery. The commercial sulindac gave a mean t_{max} of less than 2 hours. clearly indicating upper GI absorption. The area under the concentration versus time curve to a given time point represents the amount of the drug absorbed up to that time point. The ratio of that area to the total area under the concentration curve give the percentage of total drug absorbed that was absorbed up to that point. As can be seen in Table 7 the CDS formulations show relatively low absorption of the drug up to six hours, 10% and 5% respectively while treatment C, the non colonic delivery treatment, shows 87% drug delivery before six hours. One can conclude that the CDS formulations gave efficient colonic delivery. The C_{max} for the CDS formulations was considerably lower than for the commercial tablet. So was the AUC with 300 mg dosed through the CDS (treatment B) giving about 1/3 the AUC of 300 mg dosed from the commercial tablet. While one might at first glance interpret this to indicate poor absorption of the drug from the colon, an analysis of the results of the metabolites proves this to be a wrong interpretation. The AUC of the metabolites are of similar magnitude for treatments B and C, both of which had a 300 mg dose. The sulindac sulfide is somewhat higher from the CDS formulation than the conventional tablet (50.2 vs. 44.8 (h)(mg/ml)) while the sulfone is slightly

lower (27.8 vs. 32.2 (h)(mg/ml)). If the sulindac was not being absorbed in any form from the colon one would not be able to obtain the metabolites. One is forced to the conclusion that the sulindac is undergoing metabolism in the colon or colon wall and the metabolites are being absorbed and therefore found in the blood. While the C_{max} for the sulindac sulfide from the commercial sulindac is somewhat higher than that for the CDS formulation this concentration is obtained for sulindac absorbed into the blood and metabolized in the liver. The concentration seen by cells in the colon, often the target of sulindac treatment, is no higher than the blood concentration. The CDS formulation, treatment B, delivers its sulindac to the colon where the sulindac is only partially absorbed into the blood. The sulindac is metabolized in the colon and then absorbed. The concentration observed in the blood is the metabolite concentration after dilution to blood volume. It stands to reason that the concentration of the metabolite in the colon is considerably higher than that in the blood.

The metabolism of sulindac in the colon shows a preference for the sulindac sulfide over the sulindac sulfone. For equivalent doses, treatment B shows a higher AUC for sulindac sulfide than treatment C and a lower AUC for the sulindac sulfone. The ratio of AUC-sulfide/AUC-sulfone for the CDS treatment B is 1.81 while the conventional tablet of treatment C gives a ratio of 1.39. Colonic delivery, with colonic metabolism, is giving preferential metabolism to the sulfide metabolite. This preferential metabolism is probably even more pronounced than these numbers indicate. Once in the blood it is known that sulindac sulfide can be further metabolized to sulindac sulfone while the sulindac sulfone is inert (Brogden R.N., *et al.*, *Drugs 16*:97-114 (1978)). This can be seen in Table 12 where for treatment C the ratio of the average concentration of sulindac sulfide to sulindac sulfone peaks at a value of 2.73 at 4 hours and thereafter falls to values below one. The CDS treatment B shows a higher peak ratio of average sulindac sulfide to sulindac sulfone concentration of 4.04 at 12 hours after dosage. This ratio also falls due to metabolism of the sulindac sulfide to the sulindac sulfone along with elimination of both drugs from the body. The average sulindac sulfide concentration, however, stays higher than the average sulindac sulfone concentration at all time points, indicative of a continuing supply of the sulfide metabolite to the blood through metabolism of the parent sulindac in the colon.

Conclusion

It has been shown that the CDS formulations of sulindac prevent the release of sulindac in the upper GI tract and deliver the sulindac to the colon. It has been further shown that the sulindac that is delivered to the colon is metabolized in the colon to its major metabolites, sulindac sulfide and sulindac sulfone. This metabolism shows a preference for the sulindac sulfide over the sulindac sulfone. Some of the sulindac sulfone (perhaps most) is formed from the sulindac sulfide after absorption into the blood. It is inferred that the local concentration of sulindac sulfide is relatively high in the colon before absorption into the blood. Sulindac sulfide is the more active metabolite in processes that require inhibition of prostaglandin and especially in processes dependent on COX-2 inhibition. The CDS formulations described are a more efficient way of delivering the sulindac sulfide metabolite to the colon for treatment of colonic diseases such as polyps or colon cancer than conventional delivery.

What Is Claimed Is:

1. A composition or drug delivery device for localized drug release in the colon, said composition or device comprising one or more drugs in a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said composition or device enters the gastrointestinal tract, said particulate matter absorbs liquid, thus forming channels that interconnect said core with said outer surface of said coating, such that said one or more drugs are released into the colon, wherein at least one of said drugs is preferentially metabolized to a more active metabolite in the colon.

2. The composition or device of claim 1, wherein at least one of said one or more drugs is a COX-2 specific inhibitor.

3. The composition or device of claim 1, wherein at least one of said one or more drugs is a COX-1 specific inhibitor.

4. The composition or device of claim 1, wherein at least one of said one or more drugs is an anti-inflammatory drug.

5. The composition of claim 4, wherein said anti-inflammatory drug is 5-ASA (5-aminosalicylic acid) or a prodrug thereof.

6. The composition of claim 4, wherein said anti-inflammatory drug is an NSAID (non-steroidal anti-inflammatory drug).

7. The composition or device of claim 6, wherein said NSAID is selected from the group consisting of anthranilic acids, aspirin (5-acetylsalicylic acid), azodisal sodium, carboheterocyclic acids, carprofen, diclophenac, fenbufen, fenclofenac, fenoprofen, flufenamic acid, flurbiprofen, fluprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, lonazolac, loxoprofen, meclofenamic acid, mefanamic acid, naproxen, phenylacetic acids, proprionic acids, salicylic acids, salazosulfapyridine, sulindac, tolmetin, a pyrazolone butazone propazone NSAID

meloxicam, oxicams, piroxicam, feldene, piroxicam beta cyclodextran, tenoxicam, etodolac, and oxaprozin.

8. The composition or device of claim 7, wherein said NSAID is selected from the group consisting of sulindac, aspirin, diclofenac, piroxicam, meloxicam, flurbiprofen, indomethacin, ibuprofen, and fenoprofen.

9. The composition or device of claim 8, wherein said NSAID is sulindac.

10. The composition or device of claim 1, wherein said device is coated with an enteric coating.

11. The composition or device of claim 1, wherein said hydrophilic particulate matter comprises calcium pectinate

12. The composition or device of claim 11, wherein said device is coated with an enteric coating.

13. The composition or device of claim 1, wherein said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

14. The composition or device of claim 13, wherein said device is coated with an enteric coating.

15. The composition or device of claim 1, wherein said hydrophilic particulate matter comprises calcium pectinate and said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and

methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

16. The composition or device of claim 15, wherein said device is coated with an enteric coating.

17. The composition or device of claim 1, wherein said core contains a swellable agent and a disintegrating agent, and wherein said coating contains a relatively rigid hydrophobic polymer, such that upon absorption of liquid through said channels, said swellable agent swells and causes said core and said coating to burst.

18. The composition or device of claim 17, wherein said swellable core material is selected from the group consisting of polysaccharide, cross-linked polyacrylic acid, and modified cellulose.

19. The composition or device of claim 18, wherein said polysaccharide is selected from the group consisting of insoluble metal salts or cross-linked derivatives of alginate, pectin, xantham gum, guar gum, tragacanth gum, and locust bean gum, carrageenan, starch, microcrystalline cellulose, metal salts thereof, and covalently crosslinked derivatives thereof.

20. The composition or device of claim 18, wherein said modified cellulose is selected from the group consisting of cross-linked derivatives of hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose and carboxymethylcellulose and metal salts of carboxymethylcellulose.

21. The composition or device of claim 17, wherein said particulate matter comprises a polymer selected from the group consisting of a water-insoluble polysaccharide, a water-insoluble cross-linked polysaccharide, a water-insoluble polysaccharide metal salt, a water-insoluble cross-linked protein, a water-insoluble cross-linked peptide, water insoluble protein;

polysaccharide complex, a water insoluble peptide: polysaccharide complex, a polysaccharide or a protein or peptide rendered insoluble by interaction with a poly-cation or poly-anion and a water-insoluble cross-linked hydrophilic polymer in dried powder form.

22. The composition or device of claim 21, wherein said polysaccharide is selected from the group consisting of an insoluble metal salt of pectin, xantham gum, carrageenan, tragacanth gum, locust bean gum, and alginic acid; an insoluble crosslinked derivative of xantham gum, guar gum, dextran, carrageenan, tragacanth gum, locust bean gum, pectin, starch, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethyl-cellulose and alginic acid, cellulose, and microcrystalline cellulose

23. The composition or device of claim 22, wherein said insoluble metal salt of alginic acid is selected from the group consisting of calcium alginate, zinc alginate, aluminum alginate, ferric alginate, and ferrous alginate.

24. The composition or device of claim 22, wherein said insoluble metal salt of pectin is selected from the group consisting of calcium pectinate, zinc pectinate, aluminum pectinate, ferric pectinate, and ferrous pectinate.

25. The composition or device of claim 21, wherein said cross-linking is by a cross-linking agent selected from the group consisting of formaldehyde, glutaraldehyde, epichlorhydrin, diacid chloride, diacid anhydride, diisocyanates, diamines and borax.

26. The composition or device of claim 21, wherein said water insoluble cross-linked protein is selected from the group consisting of glutaraldehyde-cross-linked hydrolyzed gelatin, formaldehyde-cross-linked hydrolyzed gelatin, glutaraldehyde-cross-linked gelatin, formaldehyde-cross-linked gelatin, glutaraldehyde-cross-linked collagen and formaldehyde-cross-linked collagen.

27. The composition or device of claim 21, wherein said water-insoluble cross-linked hydrophilic polymer is a carbomer.

28. The composition or device of claim 21, wherein said water-insoluble cross-linked hydrophilic polymer is Crospovidone.

29. The composition or device of claim 17, wherein said water-insoluble carrier is ethylcellulose, said water-insoluble hydrophilic particulate is calcium pectinate, and said enteric coating is a methacrylic acid/methylmethacrylate or ethylacrylate anionic copolymer based on i) methacrylic acid and methylmethacrylate or ii) on methacrylic acid and ethylacrylate, wherein the ratio of free carboxyl groups to the ester groups is approximately 1:1.

30. The composition or device of claim 1, wherein when said liquid enters said channels of said coating, said one or more drugs is released through said channels to the colon.

31. A method for localized treatment of a colon of a subject, comprising the step of administering a composition to the subject, said composition comprising one or more drugs in a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said composition or device enters the gastrointestinal tract, said particulate matter absorbs liquid, thus forming channels that interconnect said core with said outer surface of said coating, such that said one or more drugs are released into the colon, wherein at least one of said drugs is preferentially metabolized to a more active metabolite in the colon.

32. A composition or device for localized administration of an anti-inflammatory drug for local treatment of a colon, said composition or device comprising one or more drugs in a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said composition or device enters the gastrointestinal tract, said particulate matter absorbs liquid, thus forming channels that interconnect said core with said outer surface of said coating, such that said drug is released into the colon.

33. The composition or device of claim 32, wherein said anti-inflammatory drug is 5-ASA (5-aminosalicylic acid) or a prodrug thereof.

34. The composition or device of claim 32, wherein said anti-inflammatory drug is an NSAID (non-steroidal anti-inflammatory drug).

35. The composition or device of claim 34, wherein said NSAID is selected from the group consisting of anthranilic acids, aspirin (5-acetylsalicylic acid), azodisal sodium, carboheterocyclic acids, carprofen, diclophenac, fenbufen, fenclofenac, fenoprofen, flufenamic acid, flurbiprofen, fluprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, lonazolac, loxoprofen, meclofenamic acid, mefanamic acid, naproxen, phenylacetic acids, proprionic acids, salicylic acids, salazosulfapyridine, sulindac, tolmetin, a pyrazolone butazone propazone NSAID, meloxicam, oxicams, piroxicam, feldene, piroxicam beta cyclodextran, tenoxicam, etodolac, and oxaprozin.

36. The composition or device of claim 35, wherein said NSAID is selected from the group consisting of sulindac, aspirin, diclofenac, piroxicam, meloxicam, flurbiprofen, indomethacin, ibuprofen, and fenoprofen.

37. The composition or device of claim 36, wherein said NSAID is sulindac.

38. The composition or device of claim 32, wherein said device is coated with an enteric coating.

39. The composition or device of claim 32, wherein said hydrophilic particulate matter comprises calcium pectinate

40. The composition or device of claim 32, wherein said device is coated with an enteric coating.

41. The composition or device of claim 32, wherein said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a

copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

42. The composition or device of claim 41, wherein said device is coated with an enteric coating.

43. The composition or device of claim 32, wherein said hydrophilic particulate matter comprises calcium pectinate and said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

44. The composition or device of claim 43, wherein said device is coated with an enteric coating.

45. The composition or device of claim 32, wherein said core contains a swellable agent and a disintegrating agent, and wherein said coating contains a relatively rigid hydrophobic polymer, such that upon absorption of liquid through said channels, said swellable agent swells and causes said core and said coating to burst.

46. The composition or device of claim 45, wherein said swellable core material is selected from the group consisting of polysaccharide, cross-linked polyacrylic acid, and modified cellulose.

47. The composition or device of claim 46, wherein said polysaccharide is selected from the group consisting of insoluble metal salts or cross-linked derivatives of alginate, pectin, xantham gum, guar gum, tragacanth gum, and locust bean gum, carrageenan, starch, microcrystalline cellulose, metal salts thereof, and covalently crosslinked derivatives thereof

48. The composition or device of claim 46, wherein said modified cellulose is selected from the group consisting of cross-linked derivatives of hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose and carboxymethylcellulose and metal salts of carboxymethylcellulose.

49. The composition or device of claim 45, wherein said particulate matter comprises a polymer selected from the group consisting of a water-insoluble polysaccharide, a water-insoluble cross-linked polysaccharide, a water-insoluble polysaccharide metal salt, a water-insoluble cross-linked protein, a water-insoluble cross-linked peptide, water insoluble protein: polysaccharide complex, a water insoluble peptide: polysaccharide complex, a polysaccharide or a protein or peptide rendered insoluble by interaction with a poly-cation or poly-anion and a water-insoluble cross-linked hydrophilic polymer in dried powder form.

50. The composition or device of claim 49, wherein said polysaccharide is selected from the group consisting of an insoluble metal salt of pectin, xantham gum, carrageenan, tragacanth gum, locust bean gum, and alginic acid; an insoluble crosslinked derivative of xantham gum, guar gum, dextran, carrageenan, tragacanth gum, locust bean gum, pectin, starch, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethyl-cellulose and alginic acid, cellulose, and microcrystalline cellulose.

51. The composition or device of claim 50, wherein said insoluble metal salt of alginic acid is selected from the group consisting of calcium alginate, zinc alginate, aluminum alginate, ferric alginate, and ferrous alginate.

52. The composition or device of claim 50, wherein said insoluble metal salt of pectin is selected from the group consisting of calcium pectinate, zinc pectinate, aluminum pectinate, ferric pectinate, and ferrous pectinate.

53. The composition or device of claim 50, wherein said cross-linking is by a cross-linking agent selected from the group consisting of formaldehyde, glutaraldehyde, epichlorhydrin, diacid chloride, diacid anhydride, diisocyanates, diamines and borax.

54. The composition or device of claim 50, wherein said water insoluble cross-linked protein is selected from the group consisting of glutaraldehyde-cross-linked hydrolyzed gelatin, formaldehyde-cross-linked hydrolyzed gelatin, glutaraldehyde-cross-linked gelatin, formaldehyde-cross-linked gelatin, glutaraldehyde-cross-linked collagen and formaldehyde-cross-linked collagen.

55. The composition or device of claim 49, wherein said water-insoluble cross-linked hydrophilic polymer is a carbomer.

56. The composition or device of claim 49, wherein said water-insoluble cross-linked hydrophilic polymer is Crospovidone.

57. The composition or device of claim 44, wherein said water-insoluble carrier is ethylcellulose, said water-insoluble hydrophilic particulate is calcium pectinate, and said enteric coating is a methacrylic acid/methylmethacrylate or ethylacrylate anionic copolymer based on i) methacrylic acid and methylmethacrylate or ii) on methacrylic acid and ethylacrylate, wherein the ratio of free carboxyl groups to the ester groups is approximately 1:1.

58. The composition or device of claim 32, wherein said liquid enters said channels of said coating, said one or more drugs is released through said channels to the colon.

59. A method for localized treatment of a colon of a subject with an anti-inflammatory drug, comprising the step of administering a composition to the subject, said composition comprising said anti-inflammatory drug in a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said composition or device enters the gastrointestinal tract, said particulate matter absorbs liquid, thus forming channels that interconnect said core with said outer surface of said coating, such that said anti-inflammatory drug is released into the colon.

60. The method of claim 59, wherein said anti-inflammatory drug is 5-ASA (5-aminosalicylic acid) or a prodrug thereof.

61. The method of claim 59, wherein said anti-inflammatory drug is an NSAID (non-steroidal anti-inflammatory drug).

62. A composition for localized administration of a steroidal drug for local treatment of a colon, said composition comprising a device containing one or more steroidal drugs in a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said composition enters the gastrointestinal tract, said particulate matter absorbs liquid, thus forming channels that interconnect said core with said outer surface of said coating, such that said one or more steroidal drugs are released into the colon.

63. The composition of claim 62, wherein said steroidal drug is selected from the group consisting of hydrocortisone, prednisone, prednisolone, dexamethasone, methylprednisolone, betamethasone, cortisone acetate, triamcinolone, fluoromethalone, desoximetasone, fludrocortisone acetate, cortisone, budesonide, prednisolone sodium metasulphobenzoate, tixocortol pivalate, prednisolone sodium phosphate, flunisolide, triamcinolone acetonide, flucinonide, desonide, beclomethasone dipropionate, fluticasone propionate, and hydrocortisone acetate.

64. A composition for localized administration of an anti-cancer drug for local treatment of a colon, said composition comprising a device containing one or more anti-cancer drugs in a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said composition or device enters the gastrointestinal tract, said particulate matter absorbs liquid, thus forming channels that interconnect said core with said outer surface of said coating, such that said one or more anti-cancer drugs are released into the colon.

65. The composition of claim 64, wherein said anti-cancer drug is selected from the group consisting of chlorambucil , methotrexate, irinotecan, sulindac and melphelan.

66. The composition of claim 64, wherein said device comprises a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said composition or device enters the gastrointestinal tract, said particulate matter absorbs liquid, thus forming channels that interconnect said core with said outer surface of said coating, and through which channels, said sulindac is released into said colon.

67. The composition of claim 64, wherein said device is coated with an enteric coating.

68. The composition of claim 64, wherein said hydrophilic particulate matter comprises calcium pectinate.

69. The composition of claim 64, wherein said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

70. The composition of claim 69, wherein said device is coated with an enteric coating.

71. The composition of claim 64, wherein said hydrophilic particulate matter comprises calcium pectinate and said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid

esters is 1:40; ethylcellulose; and zein.

72. The composition of claim 71, wherein said device is coated with an enteric coating.

73. The composition of claim 64, wherein said device is a tablet or capsule.

74. The composition of claim 73, wherein said tablet or capsule is coated with an enteric coating.

75. The composition of claim 74 , wherein said tablet is a matrix tablet.

76. The composition of claim 64, wherein said drug is encapsulated in a microsphere, a liposome, a nanosphere or a microemulsion.

77. The composition of claim 64, wherein said drug is in the form of pellets or minitablets.

78. The composition of claim 64, wherein said device is administered by oral delivery to the subject.

79. A composition for treating a subject with sulindac, the composition comprising sulindac in a drug delivery device for minimizing release of said sulindac in the subject prior to said sulindac reaching the colon of the subject, and that maximizes the release of said sulindac in the colon of the subject.

80. The composition of claim 79, wherein said sulindac is preferentially metabolized into sulindac sulfide.

81. The composition of claim 80 , wherein said device comprises a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said composition or device enters the gastrointestinal tract, said particulate matter absorbs

liquid, thus forming channels that interconnect said core with said outer surface of said coating, and through which channels, said sulindac is released into said colon.

82. The composition of claim 80, wherein said device is coated with an enteric coating.

83. The composition of claim 82, wherein said hydrophilic particulate matter comprises calcium pectinate.

84. The composition of claim 79, wherein said device is coated with an enteric coating.

85. The composition of claim 84, wherein said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

86. The composition of claim 79, wherein said hydrophilic particulate matter comprises calcium pectinate and said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

87. The composition of claim 79, wherein said device is a tablet or capsule.

88. The composition of claim 79, wherein said tablet is a matrix tablet.

89. The composition of claim 79, wherein said drug is encapsulated in a microsphere, a liposome, a nanosphere or a microemulsion.

90. The composition of claim 79, wherein said drug is in the form of pellets or minitablets.

91. The composition of claim 79, wherein the subject is being treated for a colonic disease.

92. The composition of claim 91, wherein said colonic disease is colon polyps or colon cancer.

93. The composition of claim 79, wherein said device is administered by oral delivery to the subject.

94. The composition of claim 93, wherein said device contains sulindac and the dose of said sulindac that is administered to the subject is 2-500 mg daily for 1-12 months in single or divided doses.

95. The composition of claim 93, wherein said device contains sulindac and the dose of said sulindac that is administered to the subject is 2-500 mg daily chronically in single or divided doses.

96. A method for treating or preventing colon polyps or colon cancer in a patient in need of the same, said method comprising administering one or more NSAIDs to said patient in a composition or device that minimizes release of at least one of said one or more NSAIDs prior to said at least one NSAID reaching said patient's colon and that maximizes the release of said at least one NSAID in said patient's colon.

97. The method of claim 96, wherein said NSAID is metabolized into a more active metabolite in said patient's colon.

98. The method of claim 96, wherein said at least one NSAID is a COX-2 specific inhibitor.

99. The method of claim 96, wherein said at least one NSAID is a COX-1 specific inhibitor.

100. The method of claim 96, wherein said at least one NSAID is selected from the group consisting of anthranilic acids, aspirin (5-acetylsalicylic acid), azodisal sodium, carboheterocyclic acids, carprofen, diclophenac, fenbufen, fenclofenac, fenoprofen, flufenamic acid, flurbiprofen, fluprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, lonazolac, loxoprofen, meclofenamic acid, mefanamic acid, naproxen, phenylacetic acids, proprionic acids, salicylic acids, salazosulfapyridine, sulindac, tolmetin, a pyrazolone butazone propazone NSAID, meloxicam, oxicams, piroxicam, feldene, piroxicam beta cyclodextran, tenoxicam, etodolac, and oxaprozin.

101. The method of claim 100, wherein said at least one NSAID is selected from the group consisting of sulindac, aspirin, diclofenac, piroxicam, meloxicam, flurbiprofen, indomethacin, ibuprofen, and fenoprofen.

102. The method of claim 101, wherein said at least one NSAID is sulindac.

103. The method of claim 100, wherein said composition or device comprises a core, and a coating surrounding said core, said coating having an outer surface, wherein said coating comprises water insoluble hydrophilic particulate matter embedded in a water-insoluble carrier, such that when said device entered the gastrointestinal tract, said particulate matter absorbs liquid, thus forming channels that interconnect said core with said outer surface of said coating, and through which channels, said NSAID is released into said colon.

104. The method of claim 100, wherein said composition or device is coated with an enteric coating.

105 . The method of claim 104, wherein said hydrophilic particulate matter comprises calcium pectinate.

106 . The method of claim 105, wherein said water-insoluble carrier comprises a dimethylaminoethlyacrylate/ethylmethacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is about 1:20; an ethylmethacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:40; ethylcellulose; and zein.

107 . The method of claim 97, wherein said NSAID is administered by oral delivery to said patient.

108 . The method of claim 107, wherein the dose of said NSAID that is administered to said patient is 2-500 mg daily for 1-12 months in single or divided doses.

109 . The method of claim 107, wherein the dose of said NSAID that is administered to said patient is 2-500 mg daily chronically in single or divided doses.

110 . A method for treating a subject suffering from a disease condition with a drug, wherein at least a portion of the disease condition is localized at a colon of the subject and at least a portion of the disease condition is localized outside of the colon of the subject, the method comprising the steps of:

(a) orally administering a composition containing the drug to the subject;

(b) releasing a majority of the drug from said composition at the colon of the subject;

(c) treating the portion of the disease condition localized at the colon with the drug;

(d) absorbing at least a portion of the drug through the colon for systemic action in the subject; and

(e) treating the portion of the disease condition localized outside of the colon with said systemically absorbed drug.

111. The method of claim 110, wherein the disease condition is a cancer of colon, and the portion of the disease condition localized outside of the colon is metastasized cancer of the colon.

112. The method of claim 111, wherein the drug is at least partially metabolized in the colon to an active metabolite.

113. The method of claim 111, wherein at least one of the drug and said active metabolite is systemically absorbed for systemic treatment.

114. The method of claim 111, wherein the drug is irinotecan.

115. The method of claim 111, wherein the drug is sulindac.

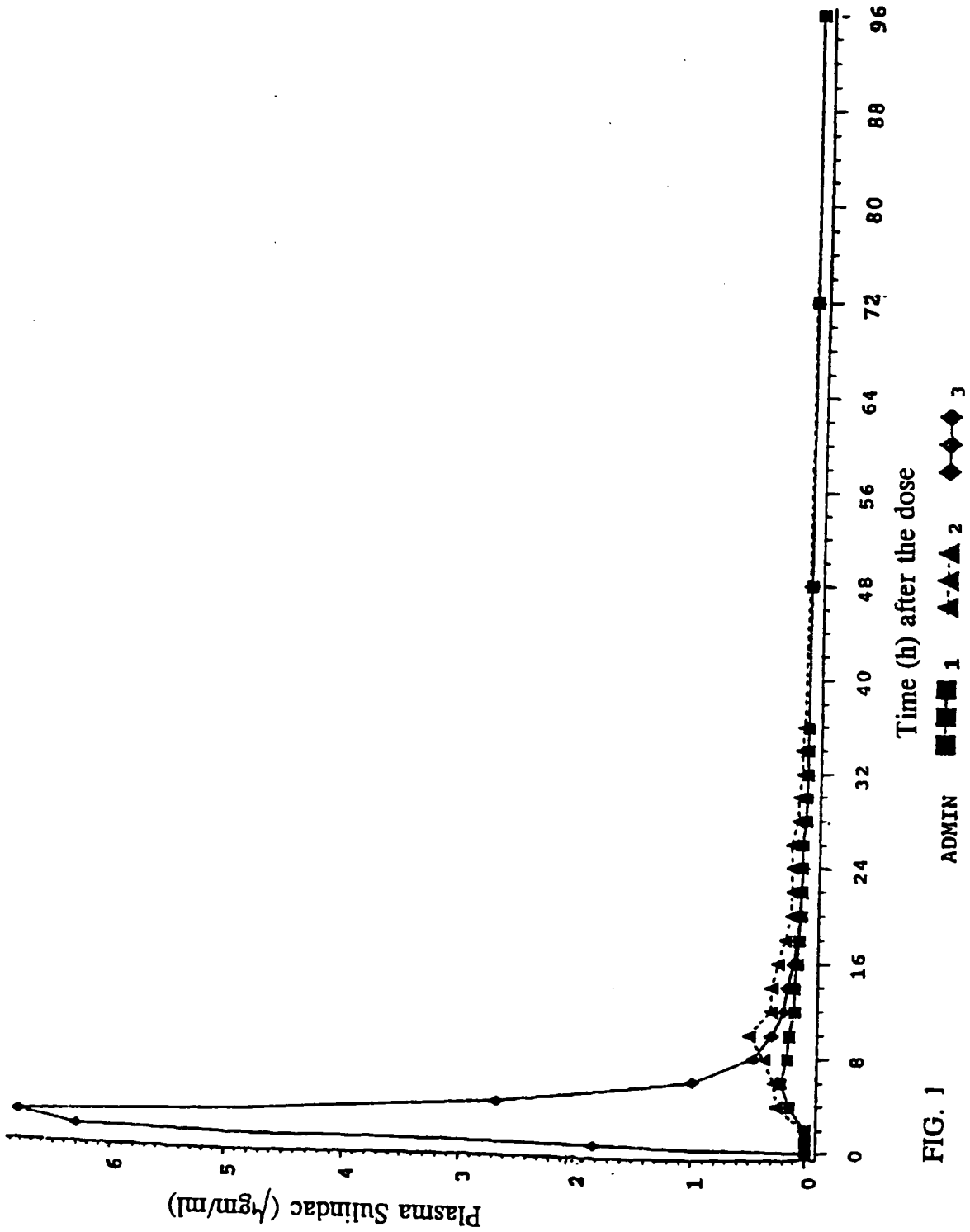
Plasma Sulindac (/gm/ml)
0
1
2
3
4
5
6
0
8
16
24
32
40
48
56
64
72
80
88
96
Time (h) after the dose
ADMIN 1 2 3

FIG. 1

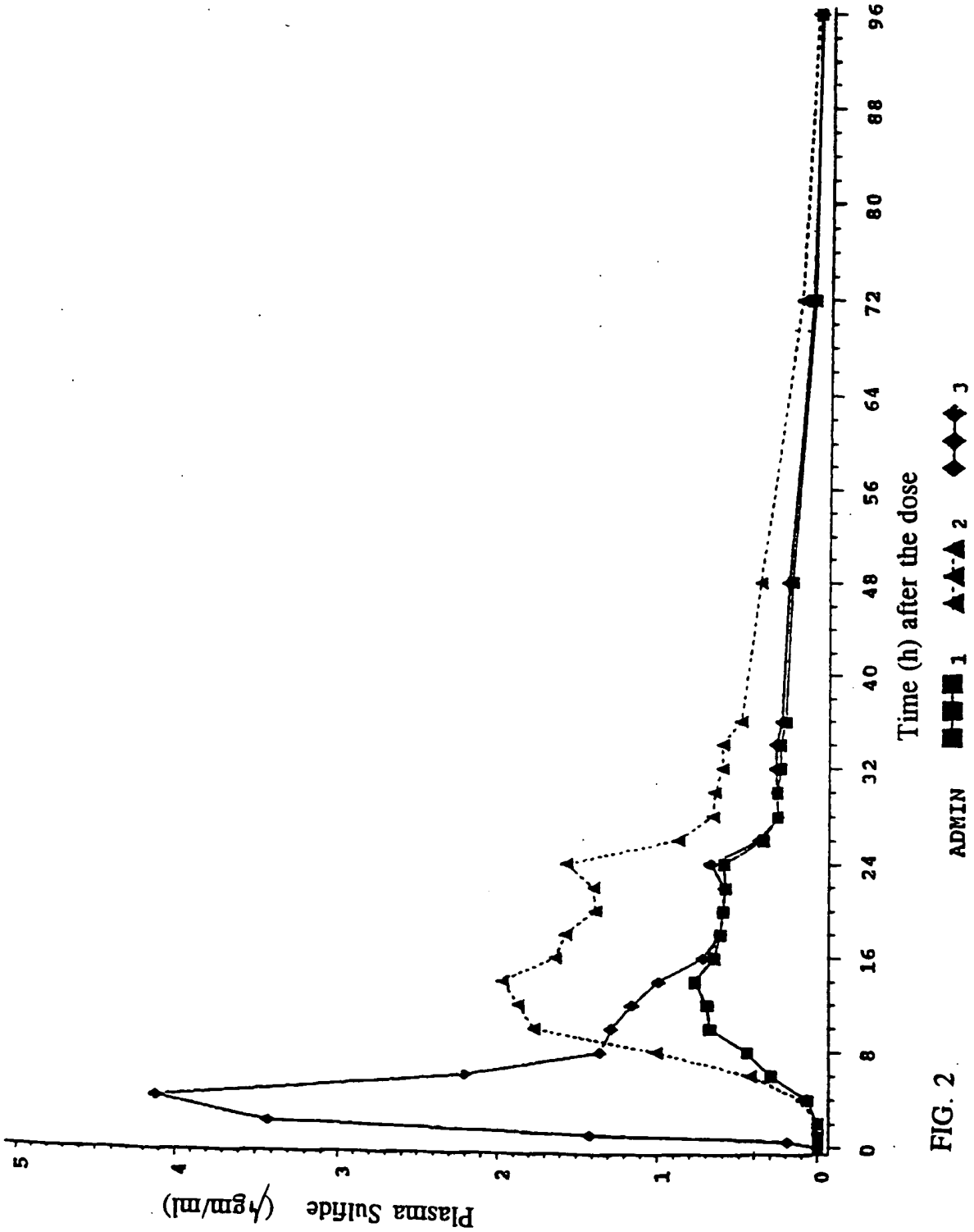
Plasma Sulfide (μgm/ml)
0
1
2
3
4
5
0
8
16
24
32
40
48
56
64
72
80
88
96
Time (h) after the dose
ADMIN 1 2 3

FIG. 2

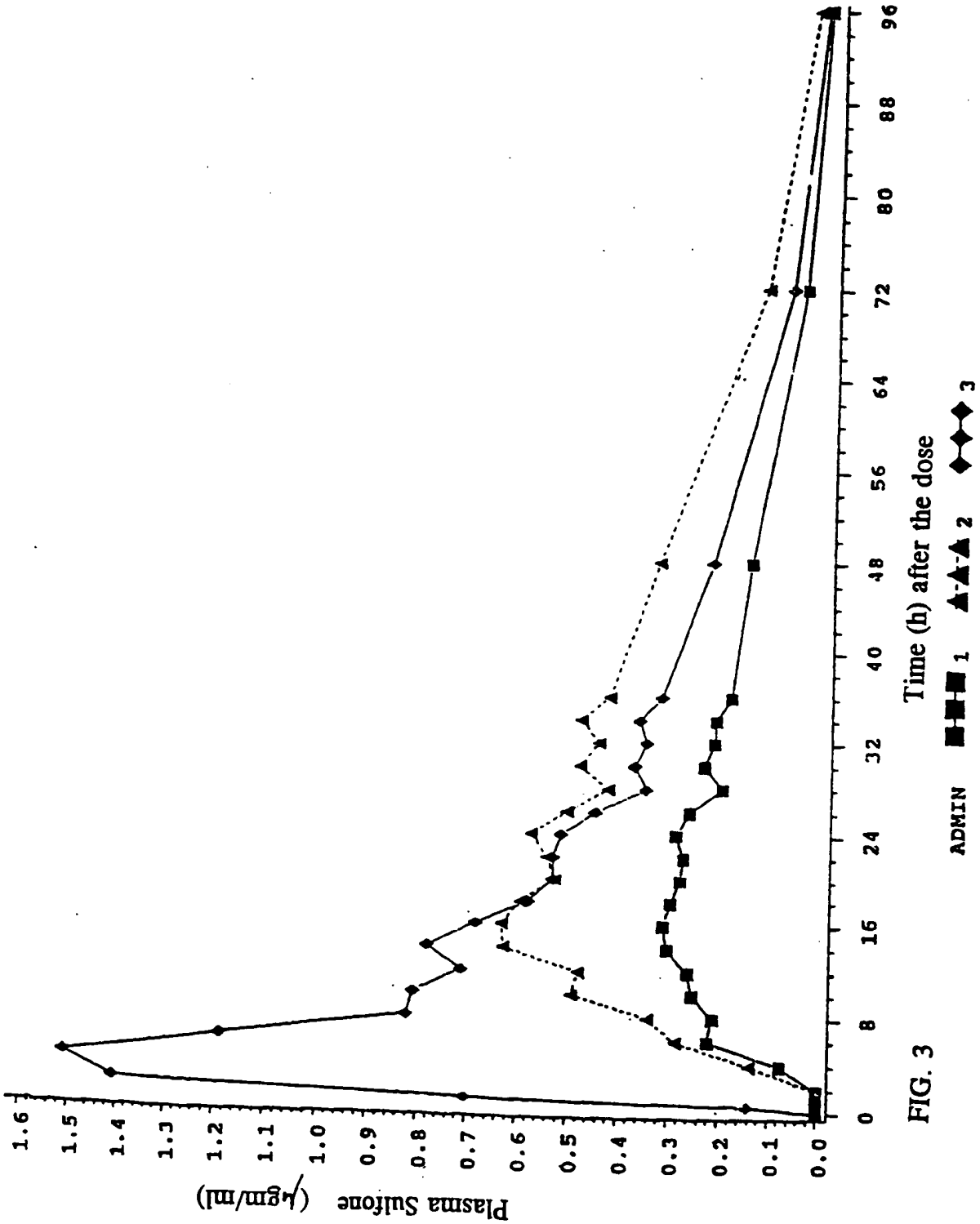
Plasma Sulfone (μgm/ml)
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
8
16
24
32
40
48
56
64
72
80
88
96
Time (h) after the dose
ADMIN 1 2 3

FIG. 3

INTERNATIONAL SEARCH REPORT

Intl. Ional Application No
PCT/IL 99/00607

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K9/28 A61K31/192 A61K31/196 A61K31/606
A61P1/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 25979 A (PERIO PROD LTD) 24 July 1997 (1997-07-24) cited in the application page 10, line 3 - line 17; claims; examples 1,3-9 page 10, last line -page 11, line 5 page 11, line 9 - line 11 page 11, line 17 - line 22 page 15, line 20 -page 16, line 1 page 16, line 13 - line 23 -/—	1-8, 10-14, 30-36, 38-40, 58-65, 67,68, 73-75, 78, 96-101, 103-105, 107, 110-113

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2000	06/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040 Tx. 31 651 epo nl	

INTERNATIONAL SEARCH REPORT

Intl. Appl. No PCT/IL 99/00607

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	page 17, line 1 - line 5 page 17, line 28 - last line page 20, line 16 - line 22 page 21, line 20 - line 22 page 22, line 1 -page 23, line 2	
X	WO 92 00732 A (KABI PHARMACIA AB) 23 January 1992 (1992-01-23) page 2, line 12 - line 36 page 3, line 19 - line 29 page 8, line 30 - line 34 page 10, line 13 -page 11, line 14; claims 1-3; example 5	1,10,30, 31,62, 63,110
X	WO 91 07949 A (NAT RES DEV) 13 June 1991 (1991-06-13) page 12, line 23 - line 31; example 4	1,4,5, 30-34, 59-61, 110
P,X, L	WO 99 18938 A (FLASHNER MOSHE ;LERNER E ITZHAK (IL); PENHASI ADEL (IL); PERIO PRO) 22 April 1999 (1999-04-22) Document so quoted for its casting doubt on the validity of the convention-priority claim. page 14, line 8 -page 15, line 22; claims 1-26,28-30,36,37; examples 1-7 page 16, line 16 - line 23 page 14, line 1 - line 3 page 24, line 18 - line 28 page 25, line 14 -page 26, line 9 page 26, line 25 - line 27 page 27, line 1 - line 2 page 28, line 8 - line 13 page 29, line 3 - line 12 page 30, line 19 - line 26 page 31, line 14 - line 23 page 32, line 15 - line 16	1-14, 17-19, 21-42, 45-56, 58-70, 73-85, 87-107, 110-113, 115

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 99/00607

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 31, 59-61, 96-115 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte cional Application No
PCT/IL 99/00607

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